

IN A WORLD
WHERE CERTAINTIES
ARE FEW...



NO WONDER
Ativan[®]
(lorazepam) 

IS PRESCRIBED BY SO MANY
CARING CLINICIANS.

Please see adjoining page for brief summary of prescribing information

THE EPIDEMIC...

DRUG ABUSE

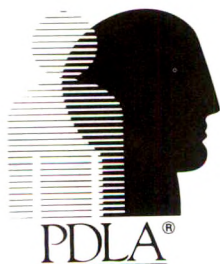
Is your hospital effectively addressing this issue?
Early detection and adequate surveillance through drug testing are essential components of contemporary medical evaluations.

Are you receiving more questions from your staff than answers from your laboratory about drug testing?
If so, you should re-evaluate the quality of your laboratory's services.

PDLA is your solution.

- Specialists in drug testing for over a decade.
- Unique analytical procedures to eliminate false negative and false positive results.
- Lowest sensitivity levels.
- Serum and urine drug levels routinely available.
- Guaranteed rapid turnaround time.
- Medical/Technical consultation.
- Complete education and training support.

For additional information about PDLA's comprehensive laboratory services for psychiatrists, please call Lynette Bates at (800) 237-PDLA.



Specialists in Psychiatric Testing

Psychiatric Diagnostic Laboratories of America, Inc.
100 Corporate Court, South Plainfield, New Jersey 07080

THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 146, Number 5 May 1989

In this issue:

Lithium Prophylaxis: Myths and Realities

By Mogens Schou

Overview of Depression and Psychosis in Alzheimer's Disease

By Robin E. Wragg and Dilip V. Jeste

An Ethnomedical Perspective of Anglo-American Psychiatry

By Horacio Fabrega, Jr.

Official Journal of the American Psychiatric Association

IN A WORLD WHERE CERTAINTIES ARE FEW...



Prompt clearance

Simple one-step metabolism

Predictable relief of anxiety

Dependable results

NO WONDER
Ativan[®]
(lorazepam)_{IV}
IS PRESCRIBED BY SO MANY
CARING CLINICIANS.

Indicate one of the following on your prescriptions, as appropriate to your state laws:

- | | |
|------------------------------------|----------------------|
| ■ Do not substitute | ■ Brand necessary |
| ■ Dispense as written | ■ May not substitute |
| ■ Medically necessary | ■ No substitution |
| ■ NDPS (no drug product selection) | |

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chloridiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.



The appearances of Ativan tablets are registered trademarks of Wyeth-Ayerst Laboratories.

**WYETH-AYERST
LABORATORIES**
Philadelphia, PA 19101

© 1989, Wyeth-Ayerst Laboratories

COLE - 102757-75-P024 370 Acc 13.11.90



THE AMERICAN JOURNAL OF PSYCHIATRY

EDITOR

John C. Nemiah, M.D.

DEPUTY EDITOR

Morris A. Lipton, Ph.D., M.D.

BOOK FORUM EDITOR

Nancy C. Andreasen, M.D., Ph.D.

EDITORIAL STAFF

Managing Editor
Melanie M. Shipley

Assistant Managing Editor
Linda A. Loy

Senior Assistant Editors
Marianne K. Guerra
Laura M. Little
Jane Weaver

Assistant Editor
Marjorie M. Henry

Production Editor
Beverly M. Sullivan

Administrative Assistant
Cynthia A. Dispenza

Editorial Secretaries
Crystal Coleman
Jennifer DuPree

ASSOCIATE EDITORS

Hagop S. Akiskal, M.D.

Ross J. Baldessarini, M.D.

Elissa P. Benedek, M.D.

Jonathan F. Borus, M.D.

Kenneth L. Davis, M.D.

Lewis L. Judd, M.D.

Toksoz Byram Karasu, M.D.

Herbert Y. Meltzer, M.D.

Judith L. Rapoport, M.D.

Loren H. Roth, M.D., M.P.H.

Lorraine D. Siggins, M.D.

Charles E. Wells, M.D.

Richard Jed Wyatt, M.D.

STATISTICAL EDITORS

John J. Bartko, Ph.D.

Lee Gurel, Ph.D.

FORMER EDITORS

Amariah Brigham, M.D.
1844-1849

T. Romeyn Beck, M.D.
1849-1854

John P. Gray, M.D.
1854-1886

G. Alder Blumer, M.D.
1886-1894

Richard Dewey, M.D.
1894-1897

Henry M. Hurd, M.D.
1897-1904

Edward N. Brush, M.D.
1904-1931

Clarence B. Farrar, M.D.
1931-1965

Francis J. Braceland, M.D.
1965-1978

The American Journal of Psychiatry, ISSN 0002-953X, is published monthly by the American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005. Subscriptions: U.S. \$56.00 (student \$28.00) per year, Canada and foreign \$71.00 (student \$43.00); single issues: U.S. \$7.00, Canada and foreign \$8.00.

Business communications, changes of address, and questions about subscriptions from APA members should be directed to the Division of Member Services: (202) 682-6090. Communications from nonmember subscribers should be directed to the Circulation Department: (202) 682-6158. Authors who wish to contact the *Journal* editorial office should call (202) 682-6020.

Business Management: Nancy Frey, Director, Periodicals Services; Laura G. Abedi, Advertising Production Manager: (202) 682-6154; Beth Prester, Director, Circulation; Karen Loper, Promotion Manager; Jackie Coleman, Fulfillment Manager.

Advertising Sales: Raymond J. Purkis, Director, 2444 Morris Avenue, Union, NJ 07083; (201) 964-3100. Steve Jones, APA, 1400 K St., N.W., Washington, DC 20005; (202) 682-6329.

Type set by Byrd Data Imaging Group, Richmond, VA. Printed by The William Byrd Press, Inc., Richmond, VA.

Second-class postage paid at Washington, DC, and additional mailing offices. POSTMASTER: Send address changes to *The American Journal of Psychiatry*, Circulation Department, American Psychiatric Association, 1400 K St., N.W., Washington, DC 20005.

Indexed in *Abstracts for Social Workers*; *Biological Abstracts*, *Chemical Abstracts*, *Chicago Psychoanalytic Literature Index*, *Cumulative Index to Nursing Literature*, *Excerpta Medica*, *Hospital Literature Index*, *Index Medicus*, *International Nursing Index*, *Nutrition Abstracts*, *Psychological Abstracts*, *Science Citation Index*, and *Social Sciences Index*.

The American Psychiatric Association does not hold itself responsible for statements made in its publications by contributors or advertisers. Unless so stated, material in the *Journal* does not reflect the endorsement, official attitude, or position of the American Psychiatric Association or of the *Journal's* Editorial Board.

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by APA for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of \$00.75 per copy is paid directly to CCC, 21 Congress St., Salem, MA 01970. 0002-953X/89/\$00.75.

This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. APA does not require that permission be obtained for the photocopying of isolated articles for nonprofit classroom or library reserve use; all fees associated with such permission are waived.

Copyright © 1989 American Psychiatric Association.

THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 146, Number 5 May 1989

SPECIAL ARTICLES

- 573 Lithium Prophylaxis: Myths and Realities *Mogens Schou*
- 577 Overview of Depression and Psychosis in Alzheimer's Disease
Robin E. Wragg and Dilip V. Jeste
- 588 An Ethnomedical Perspective of Anglo-American Psychiatry
Horacio Fabrega, Jr.

REGULAR ARTICLES

- 597 Borderline Personality Disorder, Boundary Violations, and Patient-Therapist Sex: Medicolegal Pitfalls *Thomas G. Gutheil*
- 603 Psychotherapy of Schizophrenia: An Empirical Investigation of the Relationship of Process to Outcome *Leonard L. Glass, Howard M. Katz, Robert D. Schnitzer, Peter H. Knapp, Arlene F. Frank, and John G. Gunderson*
- 609 Aberrant T Cell-Mediated Immunity in Untreated Schizophrenic Patients: Deficient Interleukin-2 Production *Françoise Villemain, Lucienne Chatenoud, André Galinowski, Françoise Homo-Delarche, Daniel Ginestet, Henri Loo, Edouard Zarifian, and Jean-François Bach*
- 617 Double-Blind Controlled Trial Comparing Carbamazepine to Oxazepam Treatment of Alcohol Withdrawal *Robert Malcolm, James C. Ballenger, Ellie T. Sturgis, and Raymond Anton*
- 622 Recent Life Events and Panic Disorder *Carlo Faravelli and Stefano Pallanti*
- 627 Lateralization of Dementia of Depression in Stroke Patients
Karen Bolla-Wilson, Robert G. Robinson, Sergio E. Starkstein, Judith Boston, and Thomas R. Price
- 635 Perinatal Loss and Parental Bereavement *Susan K. Theut, Frank A. Pedersen, Martha J. Zaslow, Richard L. Cain, Beth A. Rabinovich, and John M. Morihisa*
- 640 Influence of Nondepressive Psychiatric Symptoms on Whether Patients Tell a Doctor About Depression *Kathleen K. Bucholz and Stephen H. Dinwiddie*
- 645 Murder and Assault Arrests of White House Cases: Clinical and Demographic Correlates of Violence Subsequent to Civil Commitment *David Shore, C. Richard Filson, Wayne E. Johnson, Donald S. Rae, Peter Muehrer, Daniel J. Kelley, Ted S. Davis, Ivan N. Waldman, and Richard Jed Wyatt*
- 652 Growth Rate in Adolescents With Obsessive-Compulsive Disorder
Susan D. Hamburger, Susan Swedo, Agnes Whitaker, Mark Davies, and Judith L. Rapoport

BRIEF COMMUNICATIONS

	656	Patterns of Contagion in Self-Mutilation Epidemics	<i>Paul M. Rosen and Barent W. Walsh</i>
	659	Prevalence and Presentation of Depressive Illness in a Primary Health Care Setting in Kenya	<i>Manohar Dhadphale, Graham Cooper, and Lesley Cartwright-Taylor</i>
CLINICAL AND RESEARCH REPORTS	662	Psychopathology in Patients With Wilson's Disease	<i>Alice Medalia and I. Herbert Scheinberg</i>
	665	Posttraumatic Stress Disorder: A Descriptive Study Supporting DSM-III-R Criteria	<i>Anthony Feinstein</i>
	667	Prevalence of Posttraumatic Stress Disorder in Wounded Vietnam Veterans	<i>Roger K. Pitman, Bruce Altman, and Michael L. Macklin</i>
BOOK FORUM	670		
LETTERS TO THE EDITOR	679		
	689	Correction: J.C.N.: "New Year's Greetings"	(1989; 146:2-7)
OFFICIAL ACTIONS	690	Employee Assistance Programs and the Role of the Psychiatrist: Report of the Committee on Occupational Psychiatry	
OTHER	634	Retraction	
	644	Deceased Members of the American Psychiatric Association	
	678	ABPN Part I Written Application Deadline	
	A15	Officers of the American Psychiatric Association	
	A18	Calendar	
	A26	Books Received	
	A38	<i>British Journal of Psychiatry</i> Contents (March 1989)	
	A55	Information for Contributors	
	A60	Index to Advertisers	

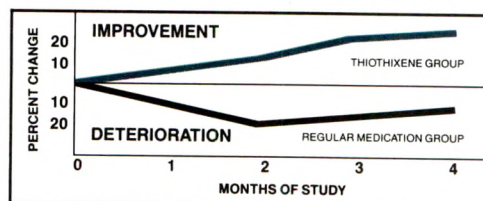


"IT FEELS GOOD TO FEEL USEFUL AGAIN"

For the chronic schizophrenic patient, Navane can mean more competent work performance,^{1,2} and a smoother path towards social recovery. Navane may help improve the ability to concentrate, and promote a better attitude toward work and co-workers.¹⁻³

Anticholinergic⁴ and cardiovascular^{5,6} side effects in patients treated with Navane are reported infrequently. Should extrapyramidal symptoms occur, they usually can be controlled.

**27% rise in work output
compared to baseline shown
in patients switched to Navane^{2,3}**

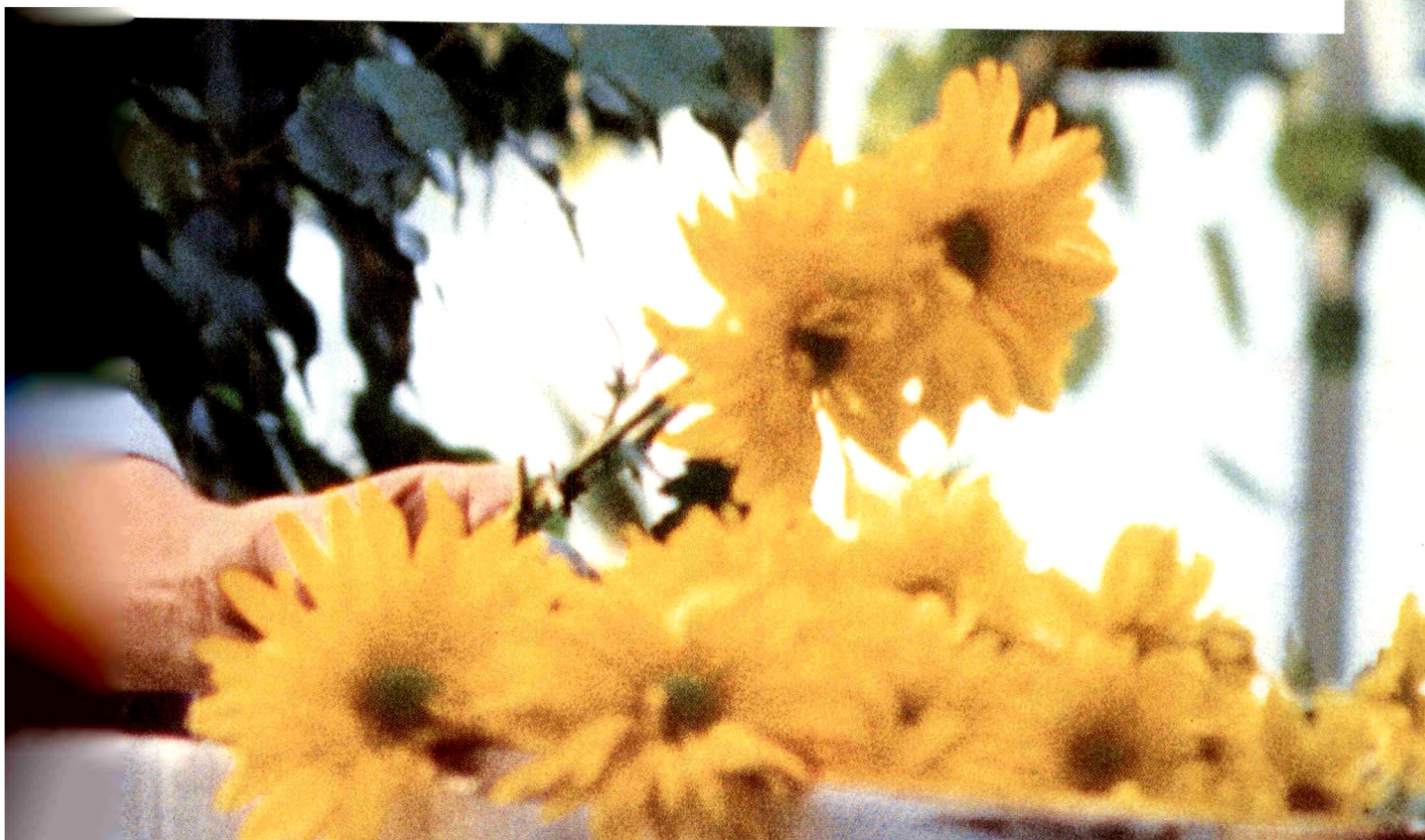


(Adapted from DiMascio and Demigian^{2,3})

Forty-two psychotic male and female patients under age 55 were entered in this study on a nonblind basis, and randomly assigned to their regular medication or switched to thiothixene. Patients were evaluated at baseline and on a daily basis, and periodically rated on the Global Improvement and Brief Psychiatric Rating Scales.

In schizophrenia,
Navane[®] (thiothixene)(thiothixene HCl)

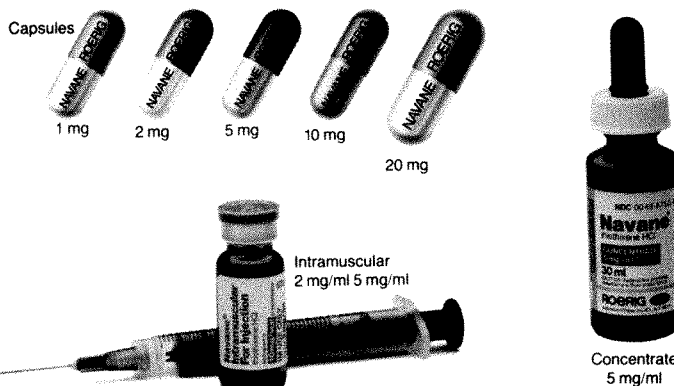
Please see brief summary of NAVANE[®] (thiothixene/thiothixene HCl) prescribing information on adjacent page.



Navane®

(thiothixene) (thiothixene HCl)

It feels good to feel useful again



References: 1. Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2. DiMascio A, Demigian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3. DiMascio A, Demigian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association, Washington, DC, May 3-6, 1971. 4. Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients. In Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry*. Basel, Switzerland, S. Karger, 1969, vol 2, pp 45-52. 5. Dillenkoff RL, Gailant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of the American Psychiatric Association, Dallas, May 1-4, 1972. 6. Data available on request from Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, **Intramuscular:** 2 mg/ml, 5 mg/ml

Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.

Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacologic treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reinstitution of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged

periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: Note: Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent tardive dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmic involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperreflexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

ROERIG

A division of Pfizer Pharmaceuticals
New York, New York 10017



No Surprises



Predictable
Rapid acting
Smooth tapering effect
Versatile
Proven safety
Unsurpassed efficacy

You've known it all along

VALIUM[®]
brand of
diazepam/Roche [®]

The cut out "V" design is a registered trademark of Roche Products Inc.

Specify "Dispense as written"



2-mg



5-mg



10-mg

scored tablets

As with any anxiolytic, patients should be cautioned against driving, operating machinery and the simultaneous ingestion of alcohol or other CNS depressant drugs.

VALIUM® (diazepam/Roche) (C)

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATED: Known hypersensitivity to the drug.

Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

WARNINGS: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

PRECAUTIONS: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is

VALIUM® (diazepam/Roche)

unclear. Inform patients to consult physician before increasing dose or abruptly discontinuing diazepam.

SIDE EFFECTS: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash; ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of diazepam; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

DOSAGE: Individualize for maximum beneficial effect. **Adults:** Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg, 1 or 2 times daily initially increasing as needed and tolerated. (See Precautions.) **Children:** 1 to 2½ mg t.i.d. or q.i.d. initially increasing as needed and tolerated (not for use under 6 months).

HOW SUPPLIED: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500. Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10.

Imprint on tablets:

2 mg—2 VALIUM® (front)
ROCHE (scored side)



5 mg—5 VALIUM® (front)
ROCHE (scored side)



10 mg—10 VALIUM® (front)
ROCHE (scored side)



Roche Products

Roche Products Inc.
Mann, Puerto Rico 00701

P.I. 0758



**THE
INSTITUTE
OF
LIVING**

400 Washington Street
Hartford, CT 06106

The 1989 Award Recipient

The Institute of Living is pleased to announce that William T. Carpenter, Jr., M.D., professor and vice chairman at The University of Maryland School of Medicine, will receive the C. Charles Burlingame Award for Psychiatric Research and Education at The Institute of Living in Hartford, Connecticut. This award honors the memory of Dr. Burlingame, psychiatrist-in-chief of The Institute of Living from 1931 to 1950.

Dr. Carpenter presently serves as vice chairman for research in the department of psychiatry at the University of Maryland and is director of the Maryland Psychiatric Research Center, where his primary research focus is on the diagnosis and treatment of schizophrenia. He has been a professor at the University of Maryland for twelve years.

Dr. Carpenter is known worldwide for his path-breaking research in schizophrenia. He has just begun a new five-year study of the treatment of patients with schizophrenia. Under his direction, one of the nation's largest clinical research fellowship programs devoted to schizophrenia outside of the NIMH Intramural Program has been developed.

With this award, The Institute of Living commends William T. Carpenter, Jr., M.D., for his outstanding contributions to our understanding of schizophrenia and psychoses, and for his dedication and leadership in psychiatric education.

**APA Annual
Meeting Attendees**

**Sandoz Pharmaceuticals
Presents:**

PHARMACOLOGIC THERAPY AND THE LONG-TERM COURSE OF SCHIZOPHRENIA

Sunday, May 7, 1989

San Francisco Hilton • Continental Ballroom
San Francisco, California

7:30 — 10:30 PM

A dinner buffet will be served at 9:45 PM following the symposium

Areas of discussion will include:

Overview of schizophrenia

Treatment options

Social functions of the treatment-resistant schizophrenic

Management of pharmacologic side effects

Psychological rehabilitation

Chairperson

Herbert Y. Meltzer, MD

Douglas Danford Bond Professor of Psychiatry
Case Western Reserve University
School of Medicine, Cleveland, Ohio

Speakers:

William T. Carpenter, Jr., MD
Director, Maryland
Psychiatric Research Center
and Professor of Psychiatry
University of Maryland
School of Medicine
Baltimore, Maryland

Dieter Naber, MD
Associate Professor of
Psychiatry
Department of Psychiatry
University of Munich
Munich, West Germany

John M. Kane, MD
Chairman, Department of
Psychiatry
Long Island Jewish
Medical Center
Professor of Psychiatry
School of Medicine, State
University of New York
Stony Brook, New York

Robert P. Liberman, MD
Professor of Psychiatry in
Residence
UCLA School of Medicine
Director of Clinical Research
Unit, Camarillo/UCLA
Chief, Rehabilitation Medical
Services
Brentwood VA Medical Center
Brentwood, California

Supported by a grant-in-aid from



Dorsey Division
SANDOZ PHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

ACCREDITATION: As an organization accredited by the ACCME to sponsor continuing medical education, the American Psychiatric Association certifies that this continuing medical education activity meets the criteria for 3 credit hours in Category I for the CME requirement of the Physician's Recognition Award of the American Medical Association and for CME requirement of the APA.

© 1989 Sandoz Pharmaceuticals Corporation

Plenum Books

NEW REFERENCES

CRITICAL ISSUES IN AMERICAN PSYCHIATRY AND THE LAW

Volume 6

CORRECTIONAL PSYCHIATRY

edited by **Richard Rosner** and **Ronnie B. Harmon**

Contributors to Volume 6 of this series address the major clinical, administrative, and legal issues surrounding forensic mental health services to jails and prisons. Topics covered include suicide, AIDS, program evaluation, privatization, treatment of personality disorders, and ethical considerations.

0-306-43070-3/320 pp./ill./1989/\$49.50

Volume 5

CRIMINAL COURT CONSULTATION

edited by **Richard Rosner** and **Ronnie B. Harmon**

For the benefit of the psychiatric consultant and lawyer, this comprehensive volume reviews clinical, administrative, and legal issues relevant to all major phases of intake, evaluation, and disposition of defendants who receive mental health services in the criminal justice system. Special attention is directed to rapport with judges, the competence of defendants to be tried, reduced criminal responsibility, police and probation issues, and expert testimony.

0-306-43061-4/344 pp./ill./1989/\$49.50

A CLINICAL GUIDE FOR THE TREATMENT OF SCHIZOPHRENIA

edited by **Alan S. Bellack**

This handbook provides an overview of current approaches to the treatment of schizophrenia, including pharmacological, psychosocial, and community approaches. The treatment strategies described are all based on new information about the nature of the disorder, its etiology, course, and special aspects that determine treatment needs.

0-306-43064-9/344 pp./ill./1989/\$39.50

text adoption price on orders of six or more copies: \$27.50

PSYCHIATRIC CONSEQUENCES OF BRAIN DISEASE IN THE ELDERLY

A Focus on Management

edited by **David K. Conn**, **Adrian Grek**, and **Joel Sadavoy**

The authors of this text review the psychiatric and behavioral consequences of various brain disorders associated with the elderly, focusing on treatment strategies and forms of management available to health care professionals.

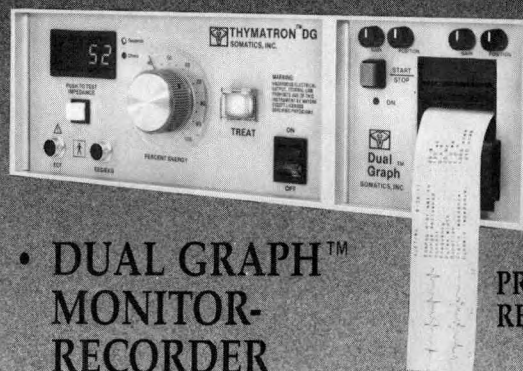
0-306-43216-1/proceedings/194 pp. + index/ill./1989 \$50.00

Book prices are 20% higher outside the US & Canada.



PLENUM PUBLISHING CORPORATION
233 Spring Street
New York, NY 10013-1578
Telephone orders: 212-620-8000/1-800-221-9369

THYMATRON™ DG



- **DUAL GRAPH™ MONITOR-RECORDER**
- **ADJUSTABLE PULSEWIDTH AND FREQUENCY**
- **CHRONA™ DIGITAL TIMER**



SOMATICS, INC.

910 Sherwood Drive, Unit 18
Lake Bluff, IL 60044

Interstate toll-free 800-642-6761

Illinois 312-234-6761

Canada toll-free 800-343-3153

THE ELECTRONIC CHART

Specifically Designed for the Psychiatric Office.

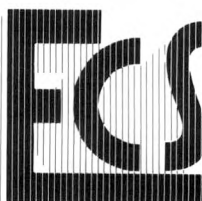
QUICK Records patient data rapidly.

SIMPLE Simple but elegant design. Easy to learn in one afternoon.

FLEXIBLE Your choice of operating environments/hardware.

PORTABLE Can carry in your portable computer.

AFFORDABLE Will pay for self in 2 years or less.

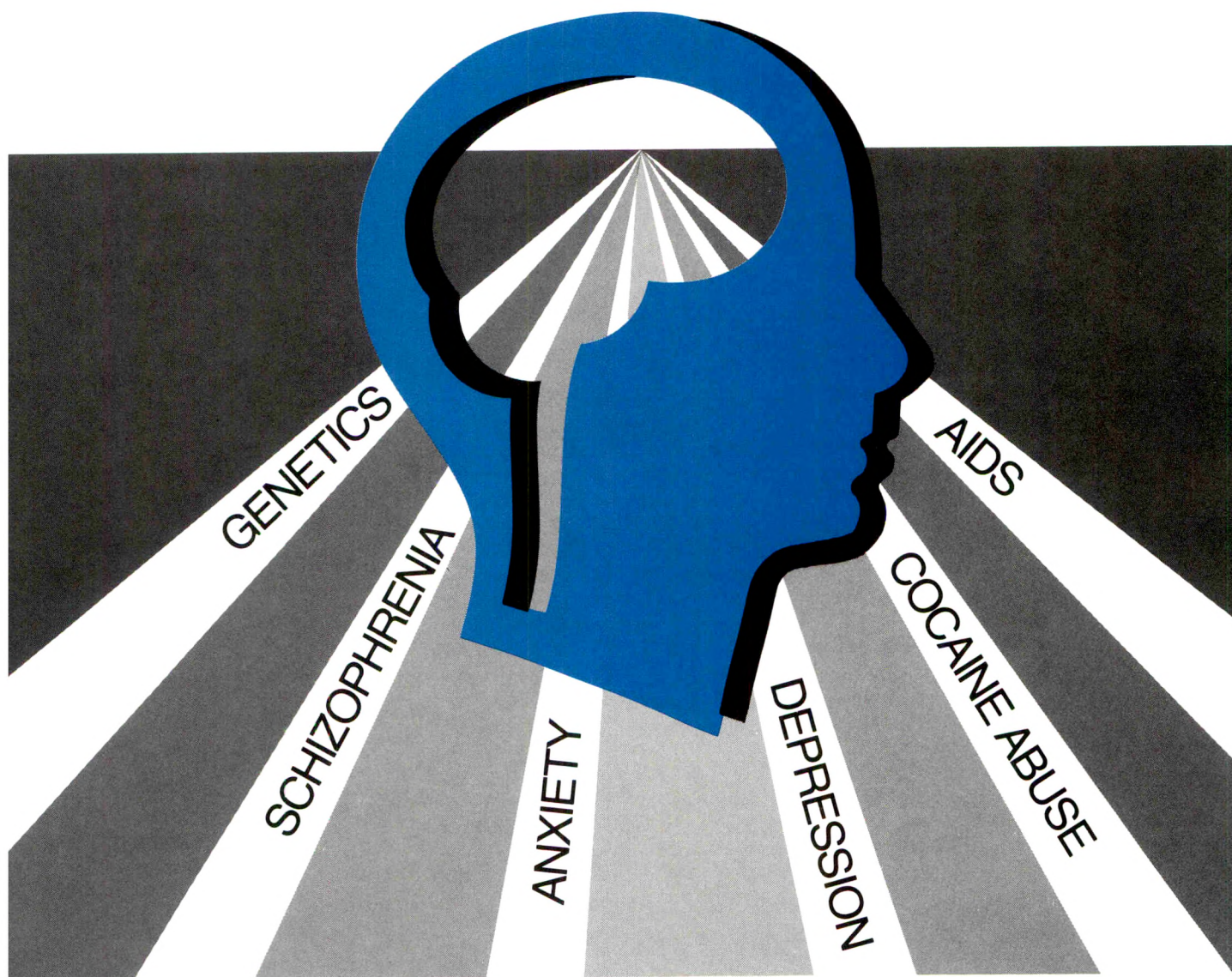


A Complete Medical Record Without Paper

THE ELECTRONIC CHART

345 Mariposa Court, Upland, CA 91786 • (714) 949-1944

NEW HORIZONS IN PSYCHIATRIC RESEARCH



Chairman:

Herbert Pardes, MD

New York Psychiatric Institute
Columbia University
College of Physicians and Surgeons
New York, New York

Psychiatric Aspects of AIDS

Frederick K. Goodwin, MD

Alcohol, Drug Abuse and Mental
Health Administration
Rockville, Maryland

New Advances in Cocaine

Abuse Treatment

Herbert D. Kleber, MD

Yale University School of Medicine
New Haven, Connecticut

New Horizons for Depression

Associated with Medical Illness

Charles Nemeroff, MD

Duke University Medical Center
Durham, North Carolina

Schizophrenia: More Than

Medical Models

Daniel R. Weinberger, MD

NIMH Neuroscience Center
Washington, DC

New Horizons for Genetics and

Mental Illness

Nancy Wexler, PhD

Columbia University
College of Physicians and Surgeons
New York, New York

TUESDAY, MAY 9, 7:00 PM—10:00 PM
CONTINENTAL BALLROOMS 4, 5, 6
SAN FRANCISCO HILTON

A buffet will be served at 5:30 p.m. before the symposium. After the program, there will be an opportunity to enjoy coffee and dessert with the speakers.

As an organization accredited by the ACCME to sponsor continuing medical education, the American Psychiatric Association certifies that this continuing medical education activity meets the criteria for 3 credit hours in Category I for the CME requirement of the Physician's Recognition Award of the American Medical Association and for the CME requirement of the APA.

© 1989, Pfizer Inc.

Supported by an educational grant from:

ROERIG **Pfizer**
A division of Pfizer Pharmaceuticals
New York, New York 10017

at the forefront of psychopharmacology

The American Psychiatric Association

1400 K Street, N.W., Washington, D.C. 20005

OFFICERS 1988-1989

President: Paul J. Fink
President-Elect: Herbert Pardes
Vice-President: Allan Beigel
Vice-President: Lawrence Hartmann
Secretary: Elissa P. Benedek
Treasurer: Alan Levenson

ASSEMBLY

Speaker: John S. McIntyre
Speaker-Elect: Gerald Flamm
Recorder: Edward Hanin

BOARD OF TRUSTEES

Robert J. Campbell III
 Frederick Gottlieb
 Shelly F. Greenfield
 Merlin Johnson
 Linda Logsdon
 Rodrigo A. Munoz
 Carol C. Nadelson
 Pete C. Palasota
 Robert O. Pasnau
 George H. Pollock
 Herbert S. Sacks
 Douglas A. Sargent
 Chester W. Schmidt, Jr.
 William L. Webb, Jr.

MEDICAL DIRECTOR'S OFFICE

Medical Director: Melvin Sabshin
Deputy Medical Directors: John M. Hamilton
 Harold A. Pincus
 Carolyn B. Robinowitz
 Jeanne Spurlock

CHAIRPERSONS OF COUNCILS, COMMISSIONS, COMMITTEES, AND TASK FORCES

CONSTITUTIONAL COMMITTEES

Budget
Constitution and By-Laws
Elections
Ethics
Tellers
Membership
Nominating
Reference
Resource Development

Steven S. Sharfstein
 Ralph A. O'Connell
 Bernice B. Elkin
 Robert J. McDewitt
 Edward C. Kirby, Jr.
 Michael J. Vergare
 George H. Pollock
 Herbert Pardes
 Howard F. Wallach

Foundations' Fund Prize for Research in Psychiatry

Grants and Awards
Manfred S. Guttmacher Award
Marie H. Eldredge Award
Hospital and Community Psychiatry Achievement Awards
Isaac Ray Award
Ittleson Award
Weinberg Memorial Award
McGavin Award
Vestmark Award
Samuel G. Hibbs Award
Advertising
Headquarters
Member Life, Accident, and Health Insurance

Ira D. Glick
 Alan I. Levenson
 William H. Reid
 Bernice E. Coleman

Doris Lee Dickens
 Richard T. Rada
 Dennis P. Cantwell
 Sanford I. Finkel
 Mina Karen Dulcan
 Bryce Templeton
 Steven M. Mirin
 Will D. Strathmann
 Raymond I. Band

COUNCIL ON AGING

Nursing Homes and Elderly Mentally Ill
Education and Training in Geriatric Psychiatry
Geriatric Psychiatry in the Public Mental Health Sector
Ethnic Minority Elderly
White House Conference on Aging
Reimbursement for Elderly Mentally Ill

Gene David Cohen
 Benjamin Liptzin
 Charles A. Shamoian
 Barry Steven Fogel
 Kenneth Mark Sakauye
 Sanford Irwin Finkel
 Howard Hirsch Goldman

Special Benefit Programs
Personnel
Advertisers and Exhibitors
Telemedical Services
History and Library
Exhibits Advisory
Friends of the APA
PIA Foundation Hospital Research Awards

Harvey Bluestone
 Abram M. Hostetter
 Maurice J. Martin
 Henry H. Work
 Jane H. Preston
 Lucy D. Ozarin
 Joseph H.B. Honnigford
 Evelyn P. Ivey-Davis
 H. Richard Lamb

COUNCIL ON CHILDREN, ADOLESCENTS, AND THEIR FAMILIES

Chronically Ill and Emotionally Handicapped Children
Confrontational Therapies
Juvenile Justice Issues
Psychiatry and Mental Health in Schools
Family Violence and Sexual Abuse
Psychiatric Aspects of New Reproductive Technologies

Larry B. Silver
 Cynthia R. Pfeffer
 Mark J. Blotcky
 William M. Buzogany
 Irving H. Berkovitz
 Sandra J. Kaplan
 Miriam B. Rosenthal

COUNCIL ON INTERNATIONAL AFFAIRS

Abuse and Misuse of Psychiatry and Psychiatrists
Inter-American Council Liaison
Human Rights
Psychosocial Aspects of the Middle East Process
International Education
Joint Meeting in Germany in 1990

Harold M. Visotsky
 Michael R. Zales
 Jorge A. Costa e Silva
 Lawrence Hartmann

COUNCIL ON ECONOMIC AFFAIRS

Financing and Marketing
JCAH Standards for Hospital-Based, Hospital-Related Services
Interprofessional Affairs
Social Security Income/Disability Insurance
Prospective Payment Issues
Future Trends in Private Insurance
Psychiatrist Payment
Quality Assurance

Donald J. Scherl
 Robert O. Friedel
 Boris M. Astrachan
 Mildred Mitchell-Bateman
 Arthur T. Meyerson
 Joseph T. English
 Robert W. Gibson
 Boris M. Astrachan
 George Wilson

COUNCIL ON MEDICAL EDUCATION AND CAREER DEVELOPMENT

Administrative Psychiatry
Medical Student Education
Graduate Education
Continuing Education
Consultation-Liaison Psychiatry and Primary Care Education
Impaired Physician
Communication Between APA and ABPN
Recertification
Independent Study
PKSAP-VI
Residents
Post Residency Fellowship Programs

Joel Yager
 Stephen L. Rachlin
 Leah Joan Dickstein
 Stefan P. Stein
 John W. Goethe
 Troy L. Thompson II
 Robert W. McDermott
 Richard I. Shader
 Joe P. Tupin
 Keith Hadley Johansen
 Gordon Darrow Strauss
 Henry Carl Emmons
 George H. Pollock

COUNCIL ON INTERNAL ORGANIZATION

Arrangements
Scientific Program
Film
Scientific and Educational Exhibits
Video
Information Systems

Ronald A. Shellow
 Kathleen Bell Unger
 Mel Blaustein
 Allan Tasman
 Bernard Martin Morenz
 Jean Patricia Goodwin
 Donald Carl Fidler
 Wandal W. Winn

APA/Burroughs Wellcome Fellowship	Roger Peele	Practice of Psychotherapy	Marcia Kraft Goin
APA/Mead Johnson Fellowship	James T. Barter	Practice Issues in Organized/Managed Care	Haroutun Babigian
APA/NIMH Minority Fellowship Program	Charles A. Pinderhughes	COUNCIL ON PSYCHIATRY AND LAW	Howard V. Zonana
Psychiatric Leadership in Public Mental Health Programs	Robert L. Leon	Confidentiality	Aron S. Wolf
Education Activities for DSM-III-R	Michael A. Fauman	Treatment Records in Child Custody Disputes	Carl P. Malmquist
COUNCIL ON NATIONAL AFFAIRS	Lindbergh S. Sata	Psychiatric Diagnoses in the Courts	Seymour L. Halleck
Abuse and Misuse of Psychiatry in U.S.	Roger Dale Walker	COUNCIL ON RESEARCH	John E. Adams
Asian-American Psychiatrists	Joyce S. Kobayashi	Electroconvulsive Therapy	Richard D. Weiner
Black Psychiatrists	Ernest A. Kendrick	Long-Term Effects of Lithium on Kidney	George R. Heninger
American Indian and Alaskan		Treatments of Psychiatric Disorders	T. Byram Karasu
Native Psychiatrists	Linda K. Cross	Tardive Dyskinesia	John Michael Kane
Foreign Medical Graduates	Walter Weintraub	Psychosocial Treatment Research	John P. Docherty
Religion and Psychiatry	Marc Galanter	Prevention Research	Robert M. Rose
Hispanic Psychiatrists	Eduardo R. Val	Biographical Directory	Robert Alan Dorwart
Women	Nada Logan Stotland	Benzodiazepine Dependency	Carl Salzman
Gay, Lesbian, and Bisexual Issues	James Paul Krajeski	Psychiatric Diagnosis and Assessment	Layton McCurdy
Occupational Psychiatry	Duane Q. Hagen	Research on Psychiatric Treatments	John M. Kane
Psychological Aspects of Nuclear Arms Development	Judith E. Lipton	DSM-IV	Allen J. Frances
Victimization	Martin Symonds	COMMISSION ON JUDICIAL ACTION	Paul Appelbaum
COUNCIL ON PSYCHIATRIC SERVICES	J. Frank James	CONSULTATION SERVICE BOARD	Dave M. Davis
Alcoholism	Richard J. Frances	ETHICS APPEALS BOARD	Elissa P. Benedek
Clinician Safety	William R. Dubin	JOINT COMMISSION ON PUBLIC AFFAIRS	Harvey L. Ruben
Drug Abuse	Edward Kaufman	JOINT COMMISSION ON GOVERNMENT RELATIONS	John J. McGrath
Rehabilitation	Arthur T. Meyerson	SPECIAL COMPONENTS	
State Mental Health Systems	Ernest W. Klatte	Board Committee on Insurance	Alan I. Levenson
American Hospital Association	Mark A. Gould	Investment Advisory Committee	Frederick Amling
Functions of the Hospital and Community Psychiatry Service, Journal, and Institute	H. Richard Lamb	Long-Range Planning Committee	Robert O. Pasnau
Institute on Hospital and Community Psychiatry Program	Leonard I. Stein	Executive Compensation Committee	William L. Webb, Jr.
Psychiatric Services for Mentally Retarded/Developmentally Disabled Adults	Ludwik S. Szymanski	Work Group on Federal Government Organizational Structure	Daniel X. Freedman
Chronically Mentally Ill	David L. Cutler	Work Group on Codes and Reimbursement	Chester W. Schmidt, Jr.
Veterans Administration Affairs	Frederick G. Guggenheim	Commission on AIDS	Stuart E. Nichols, Jr.
Private Practice	Boris G. Rifkin		
Jails and Prisons	Henry C. Weinstein		
Psychiatric Services in the Military	Leonora K. Petty		

Coming in the June 1989 issue of

THE AMERICAN JOURNAL OF PSYCHIATRY

Sleep Disturbance as the Hallmark of Posttraumatic Stress Disorder
By Richard J. Ross, William A. Ball, Kenneth A. Sullivan, et al.

Psychiatry in Africa: An Overview
By A.O. Odejide, L.K. Oyewunmi, and J.U. Ohaeri

Diagnostic Edge.

See Spectrum 32 in action
at the EEG Society Meeting,
May 6-11.



The Cadwell Spectrum 32. More objectivity in psychiatric diagnoses.

As new technologies provide more insight into brain function, psychiatry is integrating more objective data into diagnosis. The Cadwell Spectrum 32 Neurometric Analyzer provides the most comprehensive evaluation of brain electrical activity available. And gives you the diagnostic edge in corroborating a number of psychiatric disorders.

Neurometrics provides accurate differentiation.

The Spectrum 32 samples brain activity from multiple scalp locations simultaneously. Then through a process called "neurometrics," it extracts objective features and statistically evaluates these measurements relative to a normative database to detect abnormalities.



The Neurometric Analyzer goes beyond merely identifying a problem. It compares the patient's EEG profile to those of a variety of disorders, extracted from the Neurometric Psychiatric Database of more than 5000 evaluations.

Then it calculates the probability that the patient's profile corresponds to profiles characteristic of:

Learning Disabilities, Alcoholism, Dementia (Vascular vs. Non Vascular), Multiple Infarct Dementia, and Major Depression (Unipolar vs. Bipolar).

An objective adjunct to clinical diagnosis.

The Spectrum 32 provides invaluable, accurate insights into brain dysfunctions. Although it does not replace clinical diagnosis, it *does* give you objective data presented in numerical

tables, waveforms and topographic maps to support your clinical conclusions. And to help you evaluate response to treatment more precisely.

With the Spectrum 32 you not only can evaluate your own patients with new objectivity, you can also provide a referring lab service for your colleagues. Quantitative EEG measurements can be taken quickly by an EEG technologist, so you can add this service without taking too much time away from your current patients.

More than "how-to" training.

In addition to courses on neurometrics and brainmapping, Cadwell offers marketing expertise and reimbursement information. Everything you need to help you make the system *economically* — as well as *clinically* — viable.

Find out how the Spectrum 32 can give you the diagnostic edge. And how it can brighten your practice's financial picture. Call 1-800-678-6655 or 509-735-6481.

Your Clinical Link To Advanced Technology.

CADWELL®

Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.

JULY

July 1-4, annual convention, National Alliance for the Mentally Ill, "A Bridge to the Future," Cincinnati. Contact NAMI, 2101 Wilson Boulevard, Suite 302, Arlington, VA 22201; 703-524-7600.

July 4-6, annual meeting, Royal College of Psychiatrists, London. Contact Royal College of Psychiatrists, 17 Belgrave Square, London, SW1X 8PG, United Kingdom; 44-1-235-2351.

July 9-13, 10th Biennial Meeting of the International Society for the Study of Behavioral Development, Jyväskylä. Contact Department of Psychology, University of Jyväskylä, SF-4100 Jyväskylä, Finland.

July 16-21, 2nd International Conference on Health Law and Ethics, American Society of Law and Medicine, Commonwealth Lawyers' Association, and Commonwealth Medical Association, London. Contact American Society of Law and Medicine, 765 Commonwealth Avenue, Suite 1634, Boston, MA; 617-262-4990.

July 20, Institute for Addiction Studies presents "Chemical Dependency and Family Dynamics: COAs, ACAs, Myths and Issues," Oakland, California. Contact Stephanie Ross, MPI CDRH, 435 Hawthorne Avenue, Oakland, CA 94609; 415-428-4104.

July 28-29, Cook County Graduate School of Medicine presents "Psychotropic Medication—Do's and Don'ts in Everyday Clinical Practice," Chicago. Contact Francois E. Alouf, M.D.; in Illinois, 800-621-4649, outside Illinois, 800-621-4651.

July 30–August 4, 36th International Psychoanalytical Congress, Rome. Contact IPA, American Psychoanalytic Association, 309 East 49th Street, New York, NY 10017.

AUGUST

August 7-12, International Congress on "Therapy With Amino Acids and Analogues," Vienna. Contact Prof. G. Lubec, MA 17, Allgemeines Krankenhaus, Wahlinger Gurtel 18-20, 1090 Wien, Austria.

August 21-25, World Congress on Mental Health, World Federation for Mental Health, Auckland, New Zealand. Contact Richard Hunger, World Federation for Mental Health, 1021 Prince Street, Alexandria, VA 22314-2971; or Dr. M. Abbott, Mental Health Foundation, P.O. Box 37-438 Parnell, Auckland, New Zealand.

August 27–September 2, 10th International Congress, International Association of Group Psychotherapy: "Encounter or Alienation," Amsterdam. Contact Jay W. Fidler, M.D., 362 Old York Road, Flemington, NJ 08822.

August 29–September 1, 1st Congress, World Union of Professions, Montreal. Contact Services de Congres GEMS, C.P. 1016, Succ. Snowdon, Montreal, P.Q., Canada H3X 3Y1; 514-485-0855.

SEPTEMBER

September 5-8, 4th Congress of the International Psychogeriatric Association, Tokyo. Contact Akira Homma, M.D., Department of Psychiatry, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 213, Japan; 044-977-8111, Ext. 3200.

September 12-15, 3rd International Congress on Ethics in Medicine, Stockholm. Contact Third International Congress on Ethics in Medicine, Beth Israel Medical Center, 1st Avenue at 16th Street, New York, NY 10003; 212-420-4082.

September 14-16, 5th International Conference of Alzheimer's Disease International, Dublin. Contact Alzheimer's Disease International, Conference Secretariat, 12 Pembroke Park, Dublin 4, Ireland.

September 20-24, 1st European Congress of Ericksonian Hypnosis and Psychotherapy, Heidelberg, West Germany. Contact Burkhard Peter, Dipl.Psych., Milton Erickson Gesellschaft für klinische Hypnose (M.E.G.), Konradstr. 16, D-8000 München 40, West Germany; 089-2180-5175.

September 22-23, National Conference on Drug Abuse and Sport: Prevention, Intervention, Elimination, Baltimore. Contact Dr. Michael J. Asken, Chairperson, or Stephen Seitz, Coordinator, Sport Psychology Center of the Sheppard-Pratt Hospital System, P.O. Box 6815, Baltimore, MD 21285-6815; 1-800-627-0550.



When the elderly patient is taking an antidepressant, there's a chance she could end up breaking a hip.

With its low incidence of orthostatic hypotension, PAMELOR lets patients stand up with less fear of falling down.¹⁻⁷

As you know, such falls can lead to fractures, an especially serious concern for older patients. So it's important to note that, with PAMELOR, orthostatic hypotension is relatively infrequent.¹⁻⁷ In fact, in one study, patients who stopped imipramine treatment because of repeated falls experienced no such problem when switched to PAMELOR.⁵

PAMELOR has all the effectiveness of amitriptyline,⁸ as well as a low incidence of anticholinergic^{1,2,4} and sedative^{1-4,9,10} side effects.

So, measured by many standards, PAMELOR will help your elderly patients stand tall.

As with all antidepressants, patients with cardiovascular disease should be given PAMELOR only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time. Because of anticholinergic activity, PAMELOR should be used with caution in patients who have glaucoma or a history of urinary reten-

tion. PAMELOR may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating heavy machinery or driving a car; therefore, the patient should be warned accordingly.


PAMELOR[®]
(nortriptyline HCl)

The active metabolite of amitriptyline

For Brief Summary, please see following page.



PAMELOR[®]

(nortriptyline HCl)

The active metabolite of amitriptyline



All the efficacy of amitriptyline⁸ and

- low incidence of orthostatic hypotension¹⁻⁷
- little daytime sedation^{1-4,9,10}
- low incidence of anticholinergic side effects^{1,2,4}

References: 1. Thompson TL II, Thompson WL. Treating depression: tricyclics, tetracyclics, and other options. *Modern Medicine*. August 1983;51:87-109. 2. Georgiolas A. Affective disorders: pharmacotherapy. In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry IV*. Baltimore, Md: Williams & Wilkins; 1985:1821-833. 3. Blackwell B, Peterson GR, Kuzma RJ, Hostetler RM, Adolph AB. The effect of five tricyclic antidepressants on salivary flow and mood in healthy volunteers. *Communications in Psychopharmacol*. 1980;4:255-261. 4. Hayes PE, Kristoff CA. Adverse reactions to five new antidepressants. *Clin Pharm*. 1986;5:471-480. 5. Roose SP, Glassman AH, Siris SG, Walsh BT, Bruno RL, Wright LB. Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: a meaningful difference. *J Clin Psychopharmacol*. 1981;1:316-319. 6. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 7th ed. New York, NY: Macmillan Publishing Co.; 1985:413-423. 7. Thygesen P, Byrre M, Kragh-Sorensen P et al. Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology*. 1981;74:360-364. 8. Ziegler VE, Clayton PJ, Biggs JT. A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry*. May 1977;34:607-612. 9. Bye C, Clutbey M, Peck AW. Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol*. 1978;6:155-161. 10. Kupfer DJ, Spiker DG, Rossi A, Coble PA, Shaw D, Ulrich R. Nortriptyline and EEG sleep in depressed patients. *Biol Psychiatry*. 1982;17:535-546.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor[®] (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor[®] (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such

as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdose, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher AUC, and lower clearance of nortriptyline.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpromazine (250 mg/day), after the addition of nortriptyline (125 mg/day).

Adverse Reactions: Cardiovascular—Hypotension, hypertension,

tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation, insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors, peripheral neuropathy, extrapyramidal symptoms, seizures, alteration in EEG patterns, tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis, blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone marrow depression, including agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache, parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

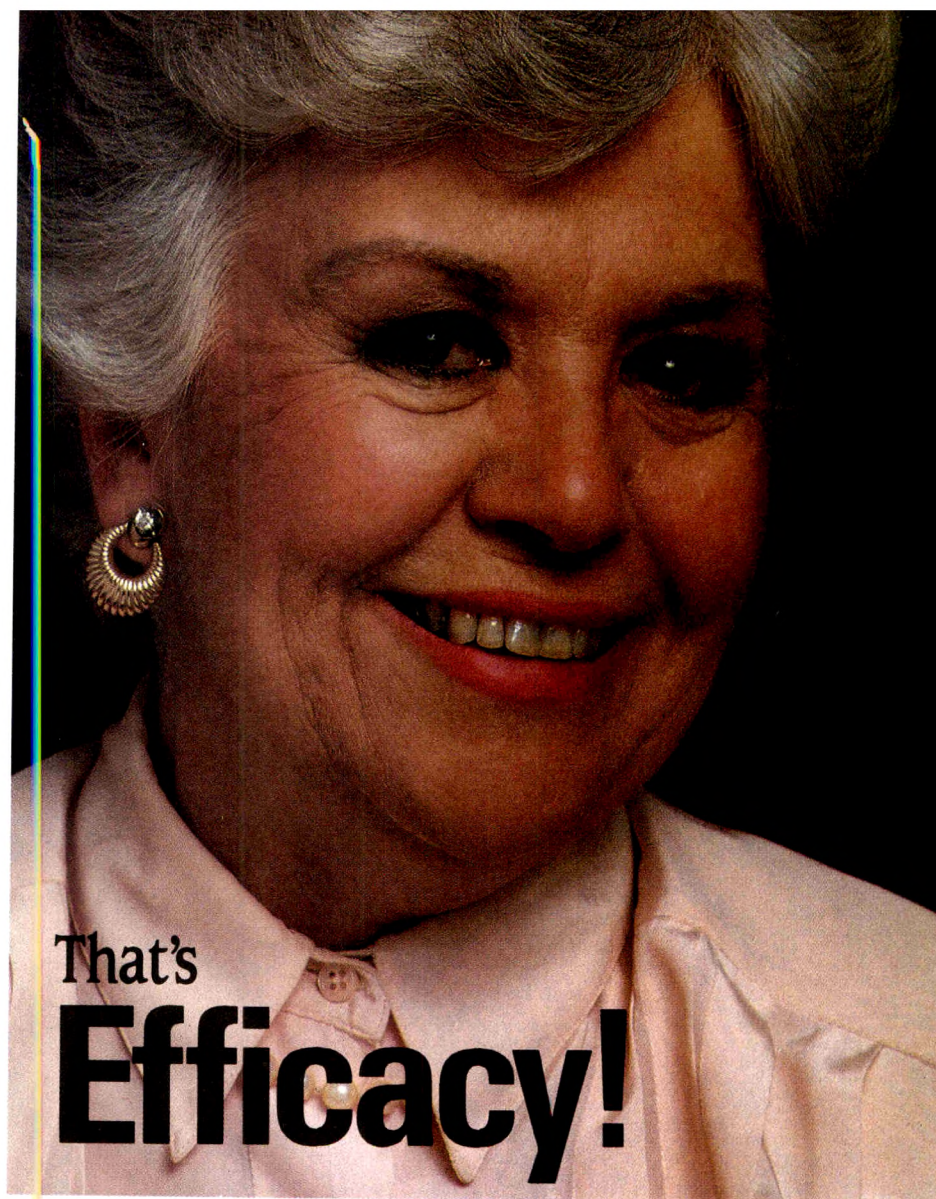
[PAM-217—1/13/89]



Sanofi Division

DORSEY PHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

Her anxiolytic
is working—
but she's alert,
functioning, and
at no risk of a
benzodiazepine
withdrawal
syndrome when
therapy ends.



That's
Efficacy!

**BuSpar relieves anxiety and returns
your patient to normal activity**

...with no more sedation (10%) than induced by placebo (9%)¹
...without inducing significant cognitive² or functional impairment*
...without producing a benzodiazepine withdrawal syndrome³
upon discontinuation

Effective choice for anxiety

BuSpar[®]
Tablets, 5 mg and 10 mg
(buspirone HCl)

for a different kind of calm



*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

For Brief Summary, please see following page.

© 1989, Bristol-Myers Company, Evansville, Indiana 47721, U.S.A.

MJL8-4270

P, 24, 370

BuSpar® (buspirone HCl)

References: 1. Newton RE, et al: A review of the side effect profile of buspirone. *Am J Med* 1986;80(33):17-21. 2. Lucki I, et al: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. 3. Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: General—Interference with cognitive and motor performance: Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/antidepressant drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B. Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): Commonly Observed—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: **Cardiovascular:** tachycardia/palpitations 1%, CNS: Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%, **EENT:** Blurred vision 2%, **Gastrointestinal:** Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%, **Musculoskeletal:** muscle aches/pains 1%, **Neurological:** Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%, **Skin:** Skin rash 1%, **Miscellaneous:** Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3300 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. **Cardiovascular—**frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. **Central Nervous System—**frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. **EENT—**frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. **Endocrine—**rare: galactorrhea, thyroid abnormality. **Gastrointestinal—**infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burring of the tongue. **Genitourinary—**infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. **Musculoskeletal—**infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. **Neurological—**infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. **Respiratory—**infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. **Sexual Function—**infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. **Skin—**infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. **Clinical Laboratory—**infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. **Miscellaneous—**infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: Controlled Substance Class—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: Signs and Symptoms—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

MJL8-4270

Mead Johnson
PHARMACEUTICALS

A Bristol Myers Company
Evansville, Indiana 47721

AMERICAN PSYCHIATRIC ASSOCIATION

A message to psychiatrists and employers

Simplify your search for the right job or job candidate. Let the professional resources of APA's Psychiatric Placement Service work for you.

If you are a psychiatrist seeking a new challenge, a better location, or a more lucrative salary, the Psychiatric Placement Service will put you in touch with suitable employers. For a modest fee and in complete confidence, you can list your professional qualifications and your personal preferences with the PPS for one year.

As an employer, you will benefit from the experience of professional recruiters who will carefully explore every aspect of your position and match your requirements against a comprehensive pool of physician candidates. Unlike other search firms, the PPS puts at your disposal the wide resources of APA—all for a fraction of the cost you might expect.

In its first year, the Psychiatric Placement Service successfully introduced many qualified candidates to prospective employers. This year, we'd like to introduce you to your next employment opportunity. Call Maureen Corrigan at (202) 682-6108 or mail this coupon today.

Please send me more information about the Psychiatric Placement Service.

☐ Potential
Applicant

☐ Potential
Employer

Name (please print)

Address

City

State

Zip

Phone

Mail to Graeme Fergusson, Placement Coordinator,
Psychiatric Placement Service, APA, 1400 K Street, N.W.,
Washington, D.C. 20005

Psychiatric Placement Service

Fully staffed and operated by the Hospital &
Community Psychiatry Service of the American
Psychiatric Association

NOW AVAILABLE!
THE 5 mL MULTI-DOSE VIAL

- ☐ same 50 mg/mL concentration
- ☐ cost-effective
- ☐ increased convenience

For the schizophrenic patient

**Sustained drug levels
with a single monthly dose**

HALDOL[®] DECANOATE
(HALOPERIDOL) INJECTION

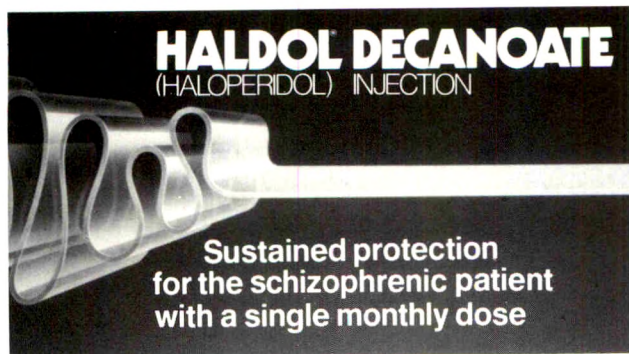
**Sustained protection
from relapse**

Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL[®] (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

 **McNEIL
PHARMACEUTICAL**
McNEILAB, INC., Spring House, PA 19477

© McNEILAB, INC., 1989



The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with NMS is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinsonian medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intracranial pressure may increase when anticholinergic drugs, including antiparkinsonian drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause

allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsome activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinsonian drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. **Withdrawal Emergent Neurological Signs—Abrupt discontinuation of short-term antipsychotic therapy** is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. **Tardive Dyskinesia—As with all antipsychotic agents** HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. **Tardive Dystonia—Tardive dystonia**, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. **Other CNS Effects—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states** which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) **Cardiovascular Effects:** Tachycardia, hypotension, hypertension and ECG changes. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Special Senses:** Cataracts, retinopathy and visual disturbances. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

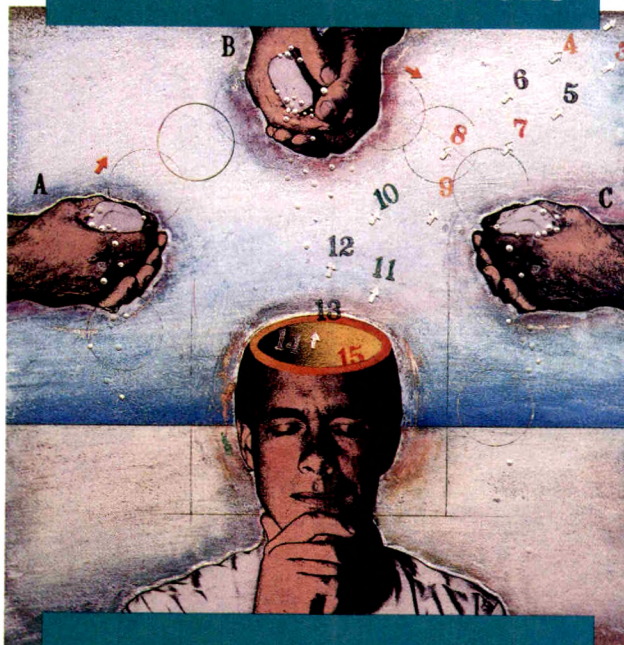
For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

7/20/88

McNEIL
PHARMACEUTICAL
McNEILAB, INC. Spring House, PA 15477

CIBA-GEIGY ANNOUNCES



A treatment IND (investigational new drug) program for patients with Obsessive- Compulsive Disorder

FDA procedures now bring promising investigational drugs to patients earlier in the development process.

The Food and Drug Administration has established procedures to allow use of "...promising drugs for treatment of patients with serious or life-threatening illnesses..."¹ as early in the drug development process as possible and before general marketing has begun.

This OCD medication is the first psychotropic drug authorized under these new procedures.

In releasing the drug for treatment use, the FDA explained that "...studies aimed at U.S. approval... have shown sufficient evidence of effectiveness for the drug to permit its limited distribution."²

For information and enrollment kits call
1-800-842-2422
between 9AM-5PM Eastern Time

Ready supply of drug available through enrolled psychiatrists for eligible patients.

The treatment medication is being distributed by CIBA-GEIGY free of charge to psychiatrists enrolled in the treatment IND program, who will, in turn, supply the drug to eligible patients.

Patient enrollment criteria established.

Patients must be between 10 and 70 years of age, with OCD symptoms of at least one year's duration that interfere significantly with daily functioning.

¹ Young FE, Benson JS, Nightingale SL, et al: Drugs available under treatment IND. *FDA Drug Bulletin* 1988;18:14-15.

²FDA Press Release, June 6, 1988.

Books Received

- Diagnosis and Treatment of Old Age Dementias**, edited by T.A. Ban and H.E. Lehmann. Basel, Karger, 1989, 102 pp., \$48.00.
- Theories on Alcoholism**, edited by C. Douglas Chaudron and D. Adrian Wilkinson. Toronto, Addiction Research Foundation, 1988, 435 pp., \$49.50 (paper).
- Countertransference Triumphs and Catastrophes**, by Peter L. Giovacchini, M.D. Northvale, N.J., Jason Aronson, 1989, 346 pp., no price listed.
- Neuropsychology and Aging: Definitions, Explanations and Practical Approaches**, edited by Una Holden. New York, New York University Press (Columbia University Press, distributor), 1988, 222 pp., \$35.00.
- The Wish for Power and the Fear of Having It**, by Althea J. Horner, M.D. Northvale, N.J., Jason Aronson, 1989, 191 pp., no price listed.
- Reshaping the Psychoanalytic Domain: The Work of Melanie Klein, W.R.D. Fairbairn, and D.W. Winnicott**, by Judith M. Hughes. Berkeley, University of California Press, 1989, 235 pp., \$30.00.
- Diagnosis and Treatment of Muscle Pain**, edited by Hans Kraus, M.D. Chicago, Quintessence Books, 1988, 111 pp., \$48.00 (paper).
- Psychiatry Around the Globe: A Transcultural View**, 2nd ed., by Julian Leff. London, Gaskell (Royal College of Psychiatrists), 1988, 222 pp., £10.00 (paper).
- What We Know About Suicidal Behavior and How to Treat It**, edited by Stanley Lesse, M.D., Med.Sc.D. Northvale, N.J., Jason Aronson, 1988, 452 pp., no price listed.
- Can We Prevent Suicide?** by David Lester. New York, AMS Press, 1989, 154 pp., \$34.50.
- Metaphoric Worlds: Conceptions of a Romantic Nature**, by Samuel R. Levin. New Haven, Yale University Press, 1988, 245 pp., \$26.50.
- Lacan in Contexts**, by David Macey. New York, Verso (Routledge, Chapman & Hall, distributor), 1988, 310 pp., \$55.00; \$18.95 (paper).
- Children of Psychiatrists and Other Psychotherapists**, by Thomas Maeder. New York, Harper & Row, 1989, 288 pp., \$19.95.
- Birth of a Self in Adulthood**, by Dorothea S. McArthur, Ph.D. Northvale, N.J., Jason Aronson, 1988, 217 pp., no price listed.
- Treatment of Patients in the Borderline Spectrum**, by W.W. Meissner, S.J., M.D. Northvale, N.J., Jason Aronson, 1988, 614 pp., no price listed.
- Left Brain, Right Brain**, 3rd ed., by Sally P. Springer and Georg Deutsch. New York, W.H. Freeman and Co., 1989, 385 pp., \$24.95; \$14.95 (paper).
- Biochemical and Pharmacological Aspects of Depression**, edited by K.F. Tipton and M.B.H. Youdim. New York, Taylor & Francis, 1989, 141 pp., no price listed.
- Coping: Maladaptation in Prisons**, by Hans Toch and Kenneth Adams with J. Douglas Grant. New Brunswick, N.J., Transaction Books, 1989, 283 pp., \$29.95.
- The Two Faces of Religion: A Psychiatrist's View**, by N.S. Xavier, M.D. Tuscaloosa, Ala., Portals Press, 1987, 211 pp., \$14.95.

In Tourette Syndrome

ORAPTM

(pimozide) Tablets

Helps Patients Be Themselves^{*}

- **Excellent Symptom Control**

"Pimozide produced significantly more improvement of symptoms and less akinesic adverse effects than haloperidol ... Improvement of 70% or more was reported by 74% of patients on pimozide compared with 45% on haloperidol ($p < .02$), and 84% rated pimozide better overall than haloperidol."¹

- **Significantly Less Sedation than Haloperidol**

In a double blind, placebo controlled study, "Pimozide was associated with lethargy or tiredness on significantly fewer days than haloperidol ($p < .01$), and this was reflected in greater immediate and long term patient acceptance ..."²

- **Documented Clinical Experience**

Pimozide has been used in the treatment of Tourette Syndrome for over 10 years.¹

- **Now Available from LEMMON**

For more information on ORAP call 1-800-523-6542, extension 246; in Pennsylvania call collect, (215) 723-5544.

The Less Sedating Therapy for Tourette Syndrome

* ORAP is indicated for patients who have failed to respond satisfactorily to standard treatment. Please see following page for a brief summary of prescribing information.

LEMMON

© LEMMON COMPANY, SELLERSVILLE, PA 18960

ORAP™ (pimozide) Tablets

The Less Sedating Therapy for Tourette Syndrome

INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and/or vocal tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment of tics that are nearly insurmountable or comorbid with depression. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and/or vocal tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 8 and 63 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

- ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than associated with Tourette's Disorder.
- ORAP should not be used in patients taking drugs that may, themselves, cause motor and/or vocal tics (e.g., neuroleptics, anticholinergics and antispasmodics) since such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
- Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
- ORAP is contraindicated in patients with severe local or central nervous system depression or convulsive states from any cause.
- ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following (see also PRECAUTIONS—Information for Patients).

Tardive Dyskinesia: A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rule out prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in the potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that in most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that: 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS—Information for Patients.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concurrent serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacologic treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug toxicity should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hypertension, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Other: Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg/kg per day. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a neuroleptic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose-related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS—Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General: ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys.

Antipsychotics should be administered with caution to patients receiving anticholinergic medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concurrently.

Laboratory Tests: An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QTc interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Serum hypokalemia has been associated with ventricular arrhythmias, potassium deficiency, secondary to diuretics, diarrhea, or other causes, should be corrected before ORAP therapy is initiated and normal potassium maintained during therapy.

Drug Interactions: Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such

as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS).

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, anxiolytics, and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about three times the maximum recommended human dose on a mg/kg basis. The mechanisms for the induction of pituitary tumors in mice is not known.

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic drug also causes elevated prolactin levels in humans. These culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains. In the mouse dominant lethal test or in the micronucleus test in rats.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

Fertility Category C: Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased preimplantation and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, notably decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks.

Labor and Delivery: This drug has no recognized use in labor or delivery.

Nursing Mothers: It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity and unknown cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited.

Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder.

ADVERSE REACTIONS

General: Extrapyramidal Reactions: Neuroleptic (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported infrequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, oculobulbar, oculogyric crises) have been reported less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Given the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinsonian drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

Tardive Dyskinesia: ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be treated.

It has been reported that few ventricular movements of the tongue may be so early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

Electrocardiographic Changes: Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, bradycardia, nodding and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizures have occurred at doses above 20 mg/day.

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS).

Hypertension: Hypertension has been reported with other antipsychotic drugs.

Clinical Trials: The following adverse reaction tabulation was derived from 20 patients in a 6 week open placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	6	1
Dysphagia	1	0
Nausea	0	2
Vomiting	0	1
Constipation	4	2
Eruptions	0	1
Thirst	1	0
Appetite increase	1	0

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Slumped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Insomnia	2	2
Dizziness	0	1
Anxiety	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Apathy	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior	5	0
Special Senses		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes	1	0
To light		
Decreased accommodation		1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

Because clinical investigations experience with ORAP in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

Other Adverse Reactions: In addition to the adverse reactions listed above, those listed below have been reported in U.S. clinical trials of ORAP in conditions other than Tourette's Disorder.

Body as a Whole: Asthenia, chest pain, periorbital edema.

Cardiovascular/Respiratory: Postural hypotension, hypotension, hypertension, tachycardia, palpitations.

Gastrointestinal: Increased salivation, nausea, vomiting, anorexia, GI distress.

Endocrine: Loss of libido.

Metabolic/Nutritional: Weight gain, weight loss.

Central Nervous System: Dizziness, tremor, parkinsonism, shivering, dyskinesia.

Psychiatric: Excitement.

Skin: Rash, sweating, skin irritation.

Serious Senses: Blurred vision, conjunctivitis.

Urogenital: Nocturia, urinary frequency.

Postmarketing Reports: The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a causal relationship with the use of ORAP.

Hematologic: Hemolytic anemia.

OVERDOSEAGE

In general, the signs and symptoms of overdose with ORAP (pimozide) would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) electrocardiographic abnormalities, 2) severe extrapyramidal reactions, 3) hypotension, 4) a comatose state with respiratory depression.

In the event of overdose, gastric lavage, establishment of a patent airway and, if necessary, mechanically-assisted respiration are advised. Electrocardiographic monitoring should commence immediately and continue until the ECG parameters are within the normal range. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinsonian medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdose.

DOSEAGE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on its manifestations in Tourette's Disorder patients below the age of twelve are not available. Consequently, the suppression of tics by ORAP requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the relief afforded is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS—Laboratory Tests).

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whether or not tics persist at the level and extent first identified. In attempts to reduce the dosage of ORAP, consideration should be given to the possibility that increases of tic intensity and frequency may represent a transient, withdrawal-related phenomenon rather than a release of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal is recommended in any case.

HOW SUPPLIED

ORAP (pimozide) 2 mg tablets, white, scored, imprint "LEMMON" and "ORAP 2—NDC 0053-0147-01, bottle of 100.

Dispense in light, light-resistant containers as defined in the official compendium.

Made in Canada

Manufactured by:
McNeil Pharmaceutical, (Canada) Ltd.

Stouffville, Ontario L4A 7x7

Printed in USA

Manufactured for:
LEMMON COMPANY

Sellersville, PA 18850

LEMMON

© 1988 LEMMON COMPANY

1. Shapiro AK et al: *Pediatrics* 79:1032-1038, 1987.

2. Ross MB et al: *Am J Psychiatry* 135:565-567, 1978.



SET THE PACE...

with your Practice.

When you launch your professional career with a HCA Psychiatric Company hospital, you will be affiliated with the nation's leading health care company. HCA needs highly qualified psychiatrists to compliment our growth and wants to talk with you.

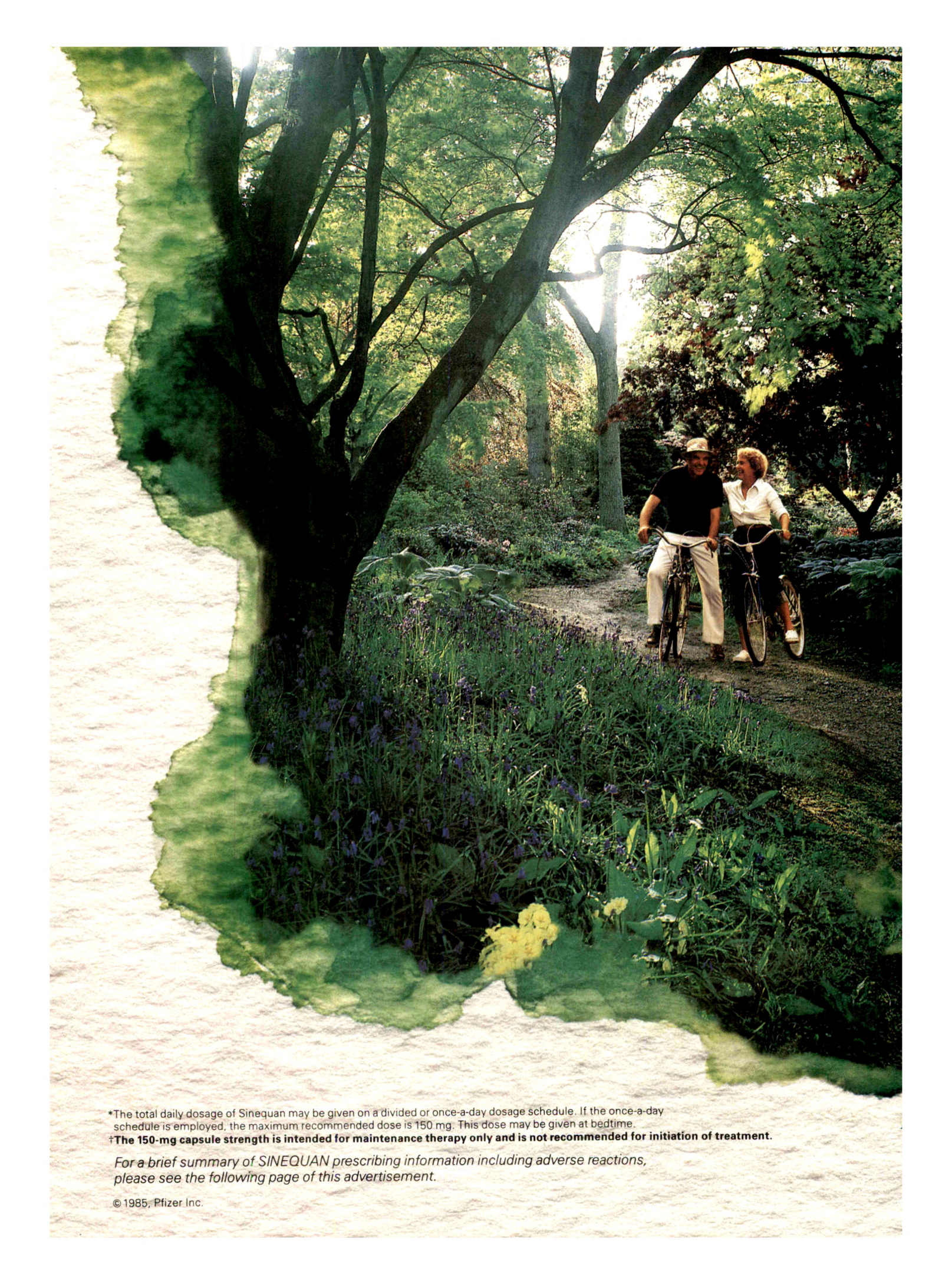
All of the opportunities available through the HCA Psychiatric Company offer attractive compensation and benefits packages. And, HCA's nationwide network of more than 65 affiliated psychiatric and chemical dependency facilities provides you with a choice of geographic location and specialties ranging from childhood/adolescent to geriatrics.

We will help link you with an existing practice or help you develop a rewarding new private practice. In addition, HCA Psychiatric Company can direct you to markets where more than 50 percent of our patients ask for physician referral.

This is the time when years of training begin to pay dividends. There are no higher quality psychiatric services or more advanced facilities than those affiliated with HCA. No one can offer you a better beginning or more opportunities to grow in your career.

For more information about our wide range of practice opportunities, contact Kyle Buster or Richard O'Donnell, HCA Psychiatric Company, One Park Plaza, P.O. Box 550, Nashville, TN 37202-0550, or call toll-free 1-800-251-2561 or 1-800-342-2110 in Tennessee.

HCA Psychiatric
Company[®]

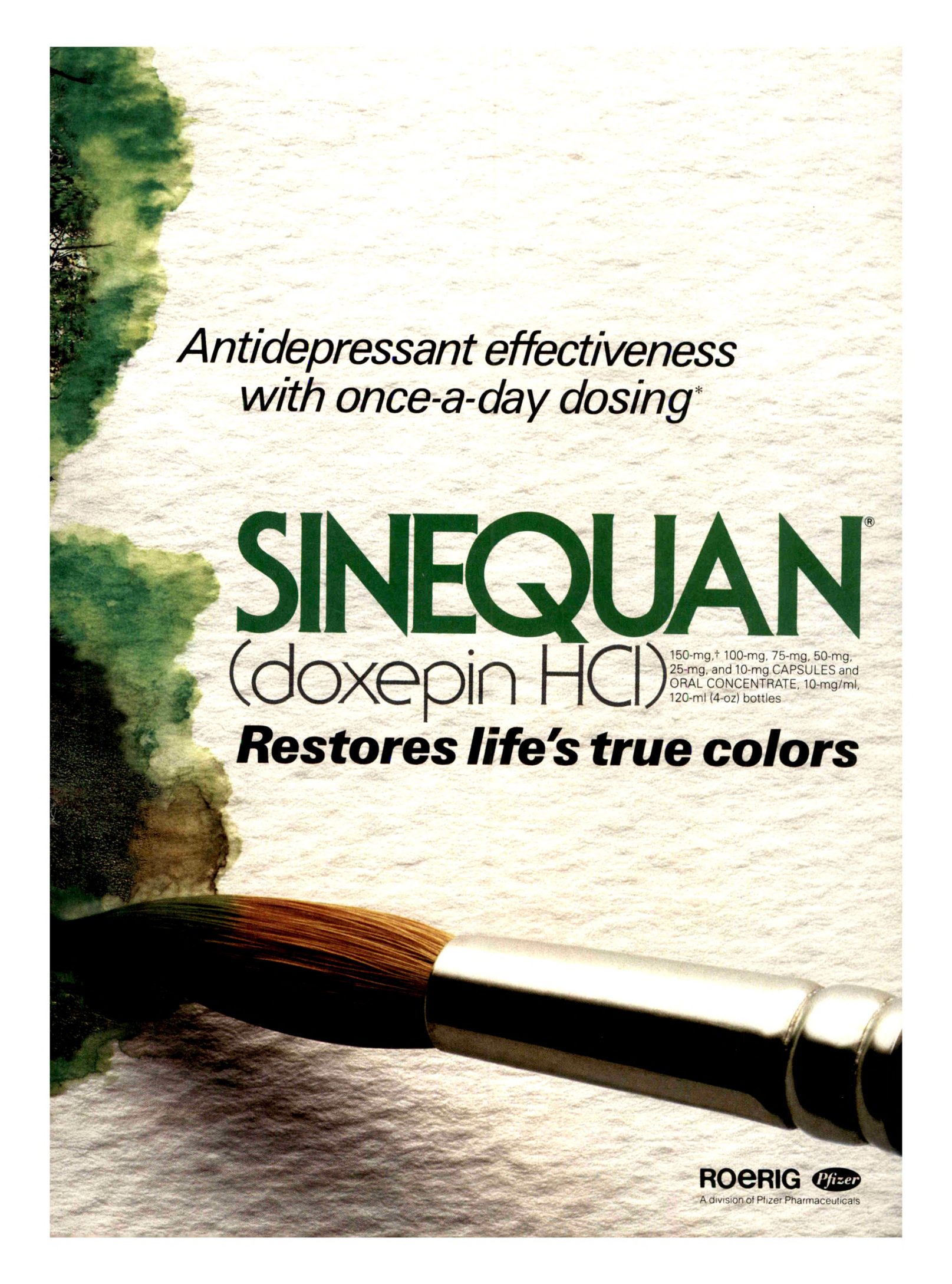


*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†**The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

© 1985, Pfizer Inc.



*Antidepressant effectiveness
with once-a-day dosing**

SINEQUAN[®]
(doxepin HCl)

150-mg,† 100-mg, 75-mg, 50-mg,
25-mg, and 10-mg CAPSULES and
ORAL CONCENTRATE, 10-mg/ml,
120-ml (4-oz) bottles

Restores life's true colors

ROERIG 
A division of Pfizer Pharmaceuticals

SINEQUAN® (doxepin HCl)

BRIEF SUMMARY

SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intermittent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

ROERIG 

A division of Pfizer Pharmaceuticals
New York, New York 10017

41st Institute on H&CP

41st Institute on H&CP

41st Institute on H&CP

41st Institute on H&CP

41st Institute on H&CP

41st Institute on H&CP

American Psychiatric Association

Philadelphia, Pennsylvania
Adams Mark Hotel

October 15-19, 1989

Please include me on the Institute's mailing list. Return to
**Sandra Hass, Dept. 189, APA, 1400 K Street, N.W., Wash-
ington, D.C. 20005 (202) 682-6174.**

Name

Address

City State Zip Code

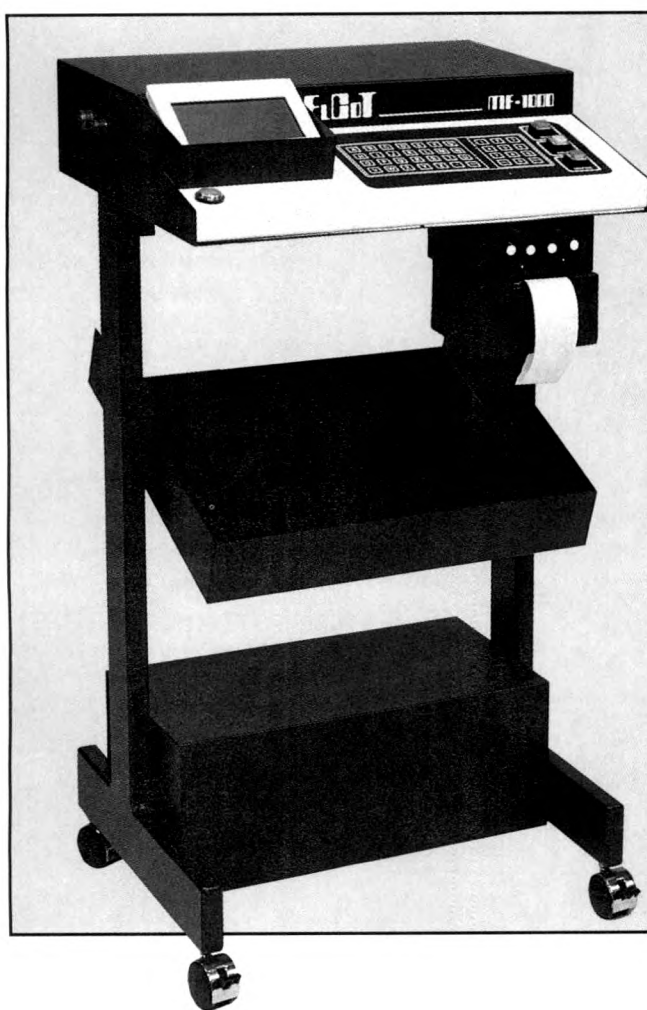
41st Institute on H&CP

41st Institute on H&CP

THE *NEW* ElCoT MF-1000

A micro-processor controlled MULTI-FUNCTION ECT unit.

Fully computerized, programmable system with **memory** for patient and treatment data of up to 500 cases, allowing the physician to choose **WAVEFORMS** (bipolar as well as unipolar positive and negative **BRIEF-PULSE** plus **SINE WAVE**) and **DOSAGE MODES** (constant current, constant voltage and constant energy) with constant automatic monitoring of real patient impedance prior to and throughout entire treatment, computer-calculated constant adjustment of all other values, ensuring the administration of stimulus values exactly as programmed by the physician.



FEATURES INCLUDE:

- Pre-programmed standard parameters in addition to complete programmability by the physician.
- 2-channel **EEG/ECG** monitoring system with strip-chart recorder also printing out all patient and treatment data
- Tiltable, "PROMPTING" large LCD for all patient and treatment data
- Impedance test and computerized safeguards to prevent treatment with parameters failing to meet recommended guidelines
- Personalized "TREAT CODE" to prevent unauthorized tampering with parameters
- Higher energy for special cases
- Possibility to interface with most personal and mainframe computers
- Fully insulated, splash-proof panel, mobile cart with accessories shelf.
- Meets or exceeds APA, RCP, IEC and UL-544 requirements.
- Complete with all accessories and User's Manual at no extra cost.

DR. MAX FINK'S
"INFORMED ECT FOR HEALTH PROFESSIONALS"
and
"INFORMED ECT FOR PATIENTS AND FAMILIES"
Video Tapes Available From ElCoT
(By Permission Of And Under License From Somatics Inc.)

CALL COLLECT or WRITE TO: ElCoT Sales, Inc.

14 East 60th Street New York, N.Y. 10022

Telephone 212-223-1300

Telex 233540

Telefax 212-755-3124

R_x

Protect Your Prescription

Specify

Dispense as Written

Mellaril[®]
(thioridazine)



Dorsey Division
SANDOZ PHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

© 1987 Sandoz Pharmaceuticals Corporation

MEL-887-1



10 mg



15 mg



25 mg



50 mg



100 mg



150 mg



200 mg



30 mg/ml



100 mg/ml



25 mg/5 ml



100 mg/5 ml

Lithium Prophylaxis: Myths and Realities

Mogens Schou, M.D.

The author examines some widely held views about prophylactic lithium treatment. When seen in relation to the factual evidence concerning lithium, these views require revision because they are wrong or not valid for treatment carried out according to present-day guidelines.

(Am J Psychiatry 1989; 146:573-576)

Lithium is used in the treatment for recurrent bipolar disorder and has helped many patients. However, it is not effective in unipolar and in rapidly cycling affective illness, in long-term use it destroys the thyroid gland and the kidneys, side effects of lithium treatment are frequent and troublesome, and lithium treatment curbs creativity. In addition, lithium intoxications can develop capriciously even with therapeutic doses and serum concentrations; when used in combination with neuroleptic drugs, lithium produces irreversible brain damage; the need for frequent laboratory monitoring makes lithium treatment cumbersome and expensive, and lithium is used too much.

These are widely held views on lithium treatment; some are not complete misconceptions. Since the treatment is administered to many patients, it behooves us to assess the extent of the truth in these statements through analysis of existing evidence or provision of new evidence.

This paper is based on the first David R. Wood Memorial Lecture, presented in Salt Lake City, May 25, 1988, and on a lecture presented in Munich at the concluding plenary session of the Collegium Neuro-Psychopharmacologicum, Aug. 19, 1988. Received July 7, 1988; accepted Oct. 26, 1988. From the Psychopharmacology Research Unit, Aarhus University Institute of Psychiatry, and The Psychiatric Hospital, Risskov, Denmark. Address reprint requests to Professor Schou, Psykiatrisk Hospital, 2 Skovagervej, DK-8240 Risskov, Denmark.

Copyright © 1989 American Psychiatric Association.

EFFECT IN UNIPOLAR ILLNESS

Doubt about the efficacy of prophylactic lithium treatment in unipolar illness seems almost exclusively a U.S. phenomenon. In other parts of the world lithium is used with good effect in recurrent unipolar affective illness, and the bulk of the published evidence clearly indicates equal prophylactic efficacy of lithium in unipolar and bipolar illness.

There are some unanswered questions here. Are American psychiatrists unable to distinguish between neurotic or chronic depressions and recurrent depressions with symptom-free intervals? Are they too impatient to wait for the sometimes gradual onset of the prophylactic action of lithium? Or is unipolar illness diagnosed differently on either side of the Atlantic? These questions need answers, for it cannot be without interest whether American unipolar patients are guarded against an ineffective drug or deprived of a valuable treatment.

EFFECT IN RAPID CYCLERS

It is true that lithium treatment often fails in manic-depressive illness with four or more episodes per year, but so do all other treatments, and no comparative trial has yet established superiority of one therapy over another. One may recall that the first observation of relapse-preventive action against depressions was made in a patient with more than 10 episodes per year (1), that in the first systematic study of lithium prophylaxis several patients had many episodes per year and yet responded satisfactorily (2), and that lithium was found highly effective in a patient who for 13 years had suffered from a 48-hour periodic psychosis (3).

These reflections are not meant to argue against trying levothyroxine, carbamazepine, or clorgyline in rapidly cycling patients. They only serve to suggest that one should give the rapid cyclers a chance also with lithium.

LONG-TERM EFFECTS ON THYROID FUNCTION

Lithium's effect on the thyroid gland was first observed in 1968 (4, 5). Recent studies have shown that in a group of lithium-treated patients there is a significant rise in mean serum thyrotropin-stimulating hormone (TSH) and a significant fall in mean serum thyroxine 6–12 months after the start of lithium treatment, but thereafter the values normalize (6, 7).

Hypothyroidism requiring treatment may arise in some patients, and reports about the frequency of this side effect range from 1% to 30%. These figures are, however, of little value when no distinction is made between incidence and prevalence. At the psychiatric hospital in Risskov my colleagues and I have carried out a systematic incidence study (6). In 202 patients who were treated with lithium for up to 6 years, hypothyroidism occurred with an incidence of 2 per 100 years of lithium exposure; the same figure has been reported from Sweden (7). All of our hypothyroid patients responded to supplementary treatment with thyroxine; this does not speak of destruction of the thyroid gland.

LONG-TERM EFFECTS ON KIDNEY FUNCTION

Observation in the 1970s of morphological kidney changes in lithium-treated patients generated grave concern among psychiatrists, who asked themselves whether the patients' mental health was bought at the expense of their kidney function and whether patients given lithium treatment for many years would eventually develop renal failure and die. Many centers decided to subject the matter to systematic scrutiny, and over the last decade the kidney function of more than 800 patients has been examined in longitudinal studies and that of more than 2,700 patients in cross-sectional studies.

The literature dealing with lithium treatment and kidney function has recently been reviewed (8), and the outcome is clear. Lithium treatment does not, even when given for many years, lead to any change of the glomerular filtration rate. After more than 35 years of lithium use in psychiatry and after treatment of large numbers of patients, not a single case of renal failure has been observed that can with any certainty be ascribed to the lithium therapy.

It was the morphological kidney changes that made such an impression in the 1970s, because they were felt to reflect severe kidney damage and a serious prognosis. The evaluation is different today (9, 10). Structural changes may occur in the glomeruli of lithium-treated patients, but they are nonspecific and can be seen also in patients about to start lithium treatment. The morphological changes that are specifically associated with lithium treatment are confined to the distal tubules and collecting ducts, are reversible, and do not signify risk of falling glomerular filtration rate or renal failure.

In recent years references to "the nephrotoxic effect

of lithium" have appeared almost routinely in discussions about and in papers dealing with prophylactic alternatives to lithium. It is time that this misleading and anxiety-inducing practice came to an end. Lithium treatment is not nephrotoxic.

THE FREQUENCY OF SIDE EFFECTS

Many side effects of lithium treatment are strongly dependent on the treatment intensity and can be avoided or reduced through use of lower doses. In 1979 at the psychiatric hospital in Risskov my colleagues and I reduced lithium doses and serum levels by about 30%. Before 1979 the average dose and serum level were 33 mmol/day and 0.85 mmol/liter, respectively; since 1979 the values have been 23 mmol/day (corresponding to a little less than 900 mg of lithium carbonate) and 0.68 mmol/liter. The frequency and intensity of lithium-induced side effects have been markedly lower after 1979 (11–13) than before (14). There has been no notable reduction of prophylactic efficacy.

Side effects have been studied longitudinally in the patients treated after 1979 (13). Complaints of tremors were presented by 5% of the patients before lithium treatment and by 15% during lithium treatment. The increase was transitory; after a few years of treatment the frequency did not differ significantly from the frequency before treatment. The patients' body weight rose, on the average, 4 kg during lithium treatment. The increase took place within the first 6–12 months; thereafter the mean body weight remained constant. Complaints of loose stools and urge to defecate rose from 1% before to 6% during lithium treatment; the frequency increased further at serum lithium levels higher than 0.8 mmol/liter.

About one-tenth of the patients presented psychological complaints, which might or might not have been caused by the lithium treatment. These complaints included memory impairment and difficulty concentrating, tiredness, "grayness of life," and, in a few cases, altered sense of taste and lowered libido or potency.

The lesson to be learned from these observations is that the physician should spend time and effort on adjusting lithium doses and serum concentrations to those levels which give the patient a maximum of prophylactic effect with a minimum of side effects. A serum lithium concentration between 0.5 and 0.8 mmol/liter is appropriate for most patients, but adjustment to values outside this range is necessary for some (15, 16). Even within the recommended range, fine individual adjustment of doses and serum levels may yield benefit; sometimes a change in serum lithium level as small as 0.1 or 0.2 mmol/liter upward or downward can make all the difference for the patient's quality of life during maintenance treatment.

EFFECT ON CREATIVITY

Lithium treatment is given to persons who suffer from recurrent manic-depressive illness, and the crucial question is whether their creativity is affected more when the illness is treated prophylactically with lithium than when it is untreated or treated with neuroleptics and antidepressants. In a study of 24 lithium-treated manic-depressive artists (17), six reported that their creativity was lower during lithium treatment than before, and four of them stopped treatment for this reason (two resumed it later). Six artists felt no change in creativity, and 12 reported that they created more and in some cases better when lithium treatment had brought their illness under control and they could work with more steadiness and better artistic discipline.

DEVELOPMENT OF INTOXICATION WITH THERAPEUTIC DOSES AND SERUM LEVELS

The occasional appearance of single-case reports about lithium intoxication in patients being treated with "therapeutic doses" seems to have left the impression that lithium poisoning can develop unexpectedly even when treatment guidelines are followed. Is that in fact so?

My colleagues and I have recently recorded all lithium intoxications that occurred over a 9-year period in the region in and around Aarhus; serum lithium determinations for this region are carried out by the laboratory at the psychiatric hospital in Risskov (18). For patients given lithium treatment in this region, the total exposure time was about 4,900 years. Lithium intoxication developed in 24 patients; none of the intoxications developed without discernible cause.

Fifteen intoxications were caused by deliberate self-poisoning with suicidal intent; no patient died. Perhaps we should impress on our patients that lithium is neither a pleasant nor a reliable self-destructive agent (19). Nine intoxications resulted from neglect of treatment guidelines. Some were caused by continued lithium treatment with unaltered dose during physical illness with fever (four cases) and during lowered intake of food and fluids in a depressive relapse (one case). One patient's physician gave him lithium doses that were too high; one patient took, in senile confusion, more lithium than prescribed; and two patients took doses that were too high because they felt good on a regimen of lithium and thought they would feel better with more lithium. No intoxication developed as a result of decreasing glomerular filtration rate.

Rather than of capriciousness, these findings speak of a high degree of predictability as far as lithium toxicity is concerned; unintended intoxications can be avoided by adherence to treatment guidelines and precautions.

RISK INVOLVED IN COMBINING LITHIUM AND NEUROLEPTICS

There is both clinical and experimental evidence that lithium and neuroleptic drugs can interact adversely. The question is whether, as has been claimed, such interaction typically leads to permanent brain damage, whether the interaction is frequent, and whether it is unavoidable. The evidence indicates that we can answer all three questions negatively.

A recent analysis of the literature led to the conclusion that permanent brain damage was no more frequent in intoxications caused by lithium given together with haloperidol than it was in intoxications caused by lithium given alone (20). Three surveys of a total of 587 patients given combination treatment with lithium and haloperidol failed to find a single instance of adverse interaction (21-23). One-third of the systematically followed Risskov patients were given neuroleptics together with lithium, and yet none showed evidence of adverse interaction (13).

The critical factor seems to be the drug dose. Lithium doses should not be higher than required to produce serum levels below 0.8 mmol/liter in most patients and between 0.8 and 1.0 mmol/liter in a few treatment-resistant ones. Haloperidol administered together with lithium should presumably not be given in doses higher than about 20 mg/day, and other neuroleptics should be given in correspondingly moderate doses. If these rules are followed, there seems to be no reason to abandon a combination therapy that is of considerable value in the treatment of acute mania and in the maintenance treatment of schizoaffective illness.

NEED FOR LABORATORY MONITORING

In our cohort study no patient developed renal failure. Increased urine volume and decreased renal concentrating ability occurred in some patients, but they did not predict deterioration of glomerular filtration rate, for there was none (12). It seems doubtful whether the time, effort, and cost of regular determinations of creatinine clearance, serum creatinine concentration, 24-hour urine volume, and renal concentrating ability are justified any longer. More important for treatment safety are the need to alert patients and relatives to risk situations (physical illness with fever, rigorous dieting, and combined treatment with lithium and diuretics or with lithium and nonsteroidal anti-inflammatory agents) and the need to instruct patients not to take more lithium than prescribed. If unusual signs and symptoms develop, patients should contact the physician, and, if the need arises, laboratory testing should be readily available.

Serum lithium determinations are presumably of sufficient use for the monitoring of lithium treatment to justify their employment at the start of treatment, after dose changes, and when lithium intoxication is suspected. It may further serve a didactic purpose and

increase compliance that serum levels are checked at appropriate intervals; the length of these intervals can be individually customized according to the patients' clinical condition, their understanding of treatment guidelines and precautions, and the need for contact between patient and psychiatrist.

Lithium-induced hypothyroidism may simulate a depressive relapse and may therefore remain undiagnosed by the psychiatrist. Determinations of serum TSH, a sensitive indicator of decreased thyroid function, may help to resolve diagnostic doubts.

THE PREVALENCE OF LITHIUM USE

Estimates have been made of how widely lithium treatment is used, but they have often been based on unreliable methods. We have recently made a detailed survey of lithium use in and around Aarhus (24). The material for analysis was provided by information about patient identity submitted together with blood samples sent to the laboratory in Risskov for serum lithium determination. We could therefore count not only the number of determinations carried out but also the number of patients actually treated.

From the total number of patients given lithium during the years 1986 and 1987, we deducted the incidence of lithium treatment, i.e., the number of patients who started lithium treatment during this period. A point prevalence of 540 in a population of 372,000 was arrived at. In other words, 1.5 of every 1,000 persons in the population had been in lithium treatment at any given time in the region under study during the period under study.

Does this mean that lithium was used too much? Or does it mean that lithium was used too little? These questions are difficult to answer. There were presumably patients who would have been better off if they had not been given this treatment, and there were in all probability patients who might have benefited if they had been given it.

In the Aarhus region, prophylactic lithium treatment has been in fairly general use for more than 15 years. This presumably means that both the phase of skeptical underuse and the phase of enthusiastic overuse have been passed, and it may not be unreasonable to assume that use of lithium by 1.5 persons of every 1,000 in the population is a reasonable estimate of the need for such therapy as used according to present-day indications.

CONCLUSIONS

The analysis presented here indicates that the opinions presented at the start of this article are not altogether wrong, for lithium treatment may be cumbersome and expensive, it may produce frequent and troublesome side effects, and it may lead to dangerous

intoxications *if it is used incorrectly*. But we need not do that. Little extra effort is required to follow the guidelines and precautions that ensure maximum efficacy and safety of lithium treatment, and our manic-depressive patients are entitled to just that.

REFERENCES

1. Schou M: Lithiumterapi ved mani: praktiske retningslinier. Nord Med 1956; 55:790-794
2. Baastrop PC, Schou M: Lithium as a prophylactic agent: its effect against recurrent depressions and manic-depressive psychosis. Arch Gen Psychiatry 1967; 16:162-172
3. Hanna SM, Jenner FA, Pearson IB, et al: The therapeutic effect of lithium carbonate on a patient with a forty-eight hour periodic psychosis. Br J Psychiatry 1972; 121:271-280
4. Schou M, Amdisen A, Jensen SE, et al: Occurrence of goitre during lithium treatment. Br Med J 1968; 3:710-713
5. Sedvall G, Jönsson B, Pettersson U, et al: Effects of lithium salts on plasma protein bound iodine and uptake of I^{131} in thyroid gland of man and rat. Life Sci 1968; 7:1257-1264
6. Maarbjerg K, Vestergaard P, Schou M: Changes in serum thyroxine (T_4) and serum thyroid stimulating hormone (TSH) during prolonged lithium treatment. Acta Psychiatr Scand 1987; 75:217-221
7. Smigan L, Wahlin A, Jacobsson L, et al: Lithium therapy and thyroid function tests: a prospective study. Neuropsychobiology 1984; 11:39-43
8. Schou M: Effects of long-term lithium treatment on kidney function: an overview. J Psychiatr Res 1988; 22:287-296
9. Walker RG, Dowling JP, Alcorn D, et al: Renal pathology associated with lithium therapy. Pathology 1983; 15:403-412
10. Walker RG, Kincaid-Smith P: Kidneys and the fluid regulatory system, in Depression and Mania: Modern Lithium Therapy. Edited by Johnson FN. Oxford, IRL Press, 1987
11. Vestergaard P, Schou M: Prospective studies on a lithium cohort, 1: general features. Acta Psychiatr Scand 1988; 78:421-426
12. Schou M, Vestergaard P: Prospective studies on a lithium cohort, 2: renal function. Water and electrolyte metabolism. Acta Psychiatr Scand 1988; 78:427-433
13. Vestergaard P, Poustrup I, Schou M: Prospective studies on a lithium cohort, 3: tremor, weight gain, diarrhea, psychological complaints. Acta Psychiatr Scand 1988; 78:434-441
14. Vestergaard P, Amdisen A, Schou M: Clinically significant side effects of lithium treatment: a survey of 237 patients in long-term treatment. Acta Psychiatr Scand 1980; 62:193-200
15. Schou M: Lithium treatment: a refresher course. Br J Psychiatry 1986; 149:541-547
16. Schou M: Lithium Treatment of Manic-Depressive Illness: A Practical Guide, 3rd ed. Basel, Karger, 1986
17. Schou M: Artistic productivity and lithium prophylaxis in manic-depressive illness. Br J Psychiatry 1979; 135:97-103
18. Schou M, Hansen HE, Thomsen K, et al: Lithium treatment in Aarhus, 2: risk of renal failure and of intoxication. Pharmacopsychiatry (in press)
19. Schou M: Long-lasting neurological sequelae after lithium intoxication. Acta Psychiatr Scand 1984; 70:594-602
20. Schou M: Adverse lithium-neuroleptic interaction: frequency, permanency, dosage dependence. Psychiatr (in press)
21. Baastrop PC, Hollnagel P, Sørensen R, et al: Adverse reactions in treatment with lithium carbonate and haloperidol. JAMA 1976; 236:2645-2646
22. Juhl RP, Tsuang MT, Perry PJ: Concomitant administration of haloperidol and lithium carbonate in acute mania. Dis Nerv Syst 1977; 38:675-676
23. Caliri B, Terenzoni B, Reginaldi D, et al: Tossicità del trattamento combinato litio-serenase. Rass Studi Psychiatr 1983; 72: 309-312
24. Vestergaard P, Schou M: Lithium treatment in Aarhus, 1: prevalence. Pharmacopsychiatry (in press)

Overview of Depression and Psychosis in Alzheimer's Disease

Robin E. Wragg, M.D., and Dilip V. Jeste, M.D.

The authors reviewed 30 studies on Alzheimer's disease to determine the prevalence and phenomenology of affective and psychotic symptoms in patients with this disorder. Depressive and psychotic symptoms occurred in 30%–40% of the Alzheimer's disease patients. Isolated symptoms were two to three times as frequent as diagnosable affective or psychotic disorders. Paranoid delusions were the most common psychotic symptoms reported. Implications of the relationship of psychiatric symptoms to the clinical presentation of Alzheimer's disease, patterns of cognitive dysfunction, clinical management, and areas for future research are discussed.

(Am J Psychiatry 1989; 146:577–587)

As the U.S. population as a whole becomes more elderly, dementia is becoming an increasingly frequent problem confronted by the general psychiatrist. Alzheimer's disease alone accounts for approximately 60% of all cases of dementia in patients over age 65 (1). In his initial case report, Alzheimer (2) described a 51-year-old woman with memory loss, disorientation, apraxia, depression, and persecutory delusions as well as delusional jealousy. Standard textbooks (3) and reviews in both the psychiatric and neurologic literature (1, 4, 5) acknowledge the occurrence of affective and psychotic features in patients with Alzheimer's disease. Nonetheless, despite increasing interest in the biological basis of affective disorders and schizophrenia, there has not been a corresponding interest in the meaning and mechanisms of affective and psychotic symptoms in known brain disorders such as Alzheimer's disease. Consequently, no consensus exists about the prevalence, phenomenology, and implications of these symptoms in Alzheimer's disease.

This paper reviews studies of psychiatric symptoms

in patients with Alzheimer's disease to assess 1) the prevalence of affective and psychotic symptoms, 2) demographic and clinical variables that may be associated with the development of such symptoms, and 3) the relationship of these symptoms to the level and pattern of cognitive dysfunction. The rationale for clarifying these questions is clinical as well as theoretical. Psychiatric symptoms, when they occur, are distressing to both the patient and his or her family or other caregivers. In interviews with the families and other primary caregivers of demented patients, Rabins et al. (6) found that psychotic symptoms (hallucinations, delusions) were present in approximately 50% of the patients and disruptive behaviors (physical violence, hiding things, wandering, or demanding or critical behavior) in up to 70%. The caregivers cited these symptoms as constituting serious problems that materially affected the quality of life for both patient and caregiver. Previous studies of demented elderly patients have suggested that even modest improvement in troublesome symptoms may result in substantial improvement in function and in quality of life (7). In contrast, unmodified behavioral symptoms may be the critical factor in the decision to institutionalize a patient (8).

Research during any given period generally reflects the fashions and standards of its era. Consequently, published studies of psychiatric symptoms in Alzheimer's disease have varied greatly in their objectives and design characteristics. Most of the investigations have been cross-sectional and descriptive in overall design, precluding the assessment of incidence or risk related to specific factors. Before 1980, most of the studies relied on retrospective chart reviews; since 1980, a large majority of the studies have used direct evaluation of patients. Similarly, the sophistication of research design and execution has improved, although several problems continue to be common. Broadly, these problems involve the study sample, methods of assessment, and data analysis and interpretation.

Problems involving the study sample relate to case definition, source of subjects, subject selection, sample size, and control subjects. Case definition has been complicated by the absence of a clinical "gold standard" for Alzheimer's disease. However, the development of both *DSM-III-R* and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (5)

Presented in part at the 140th annual meeting of the American Psychiatric Association, Chicago, May 9–14, 1987. Received Feb. 2, 1988; revision received Aug. 18, 1988; accepted Sept. 9, 1988. From the Department of Psychiatry, University of California, San Diego, and the San Diego VA Medical Center. Address reprint requests to Dr. Wragg, Department of Psychiatry, 116A, VA Medical Center, Highland Drive, Pittsburgh, PA 15206.

Supported in part by the Veterans Administration.

The authors thank Joel Dimsdale, M.D., Daniel Kripke, M.D., and Sidney Zisook, M.D., for their comments on an earlier version of this manuscript.

has brought some measure of reliability to the diagnosis of Alzheimer's disease.

No consistent source of subjects has predominated in published studies. Patients have been drawn from the entire spectrum of psychiatric and medical settings on the basis of varied inclusion criteria, which has resulted in similarly varied outcome and, thus, poor generalizability. Furthermore, subjects may have been referred expressly for evaluation or management of a neuropsychiatric or behavioral target symptom (9, 10) rather than selected from samples representing demented populations "at risk" for such complications, which would result in unrealistic estimates of prevalence. Bias in subject selection due to the absence of expressed exclusion criteria may also result in misclassification, obscuring prevalence and risk associations.

Sample sizes have often been small or insufficient for the study design. Inappropriate sample size may affect both the validity (type I or type II errors) and the strength of the inferences drawn from a study. Among the studies we reviewed, the median sample size was 33 Alzheimer's disease subjects (range=9-175). In the studies that included them, normal control subjects or comparison groups of other demented patients constituted even smaller samples.

Finally, selection of control subjects should be appropriate to the questions being studied. Ideally, studies of affective and psychotic psychopathology in Alzheimer's disease would include age-matched "normal" (i.e., not cognitively or psychiatrically impaired) control subjects or "at-risk" comparison groups (e.g., patients with dementias other than Alzheimer's disease, psychiatric patients with comparable psychopathology) drawn from the same source as the case subjects. The more recent studies from longitudinal research projects on dementia and aging (11-14) have incorporated these strategies.

Methods of assessment of psychiatric symptoms (e.g., clear and consistent definition of target symptoms, how and by whom they are ascertained) may materially affect the outcome of a study. Consequently, it is now standard practice to use rating instruments to enhance precision, reliability, and generalizability in research studies. However, rating instruments routinely used for assessing psychopathology in general adult populations may have unproven validity in relevant populations, such as elderly normal control subjects, cognitively impaired patients, and so on. Some of the advantage of using these instruments may therefore be reduced.

Data analysis and interpretation have been complicated by several factors. First, in many studies, despite precise reporting of the frequency of psychiatric symptoms and the proportion of Alzheimer patients in a sample, it is not always possible to identify those patients who have both Alzheimer's disease and psychiatric symptoms. Second, in studies of a particular symptom, the size of the appropriate at-risk comparison group may be obscure or unavailable. These problems may limit both the validity and the strength of the inferences drawn.

METHOD

We performed a computerized MEDLINE search for English-language citations of Alzheimer's disease, presenile dementia, or senile dementia *and* affective disorders, cognition disorders, paranoid disorders, or psychosis. These categories were defined as specified by the medical subject headings of that database. Because MEDLINE indexing does not include materials before 1966, we used the bibliographies of the initial retrievals to identify articles from older sources.

To limit the impact of the methodological issues we have described, only articles specifically reporting data on patients with Alzheimer's disease, presenile dementia, or senile dementia *and* affective or psychotic symptoms were selected for review. Publications not reporting new data and case reports were excluded. Some description of the method of diagnosing Alzheimer's disease (e.g., pathology reports, clinical consensus, *DSM-III*) and of the source of patients was required for inclusion. Standardized delineation of the psychiatric target symptoms (e.g., by rating scales) was desirable; however, this was the exception rather than the rule. We accepted any description of symptoms sufficient to categorize "depression" as depressed mood, major depression, or dysthymic disorder and "psychosis" as hallucinations, paranoid delusions, etc. When target symptoms were well-described but difficult to categorize other than as "psychotic," we assigned these symptoms to the category "psychotic, not otherwise specified." We identified 30 published reports that met these criteria for review.

RESULTS

Affective Symptoms

Investigations of the frequency of affective symptoms in patients with Alzheimer's disease evaluated either a specific symptom, such as depressed or elevated mood, or a specific disorder, such as major depression or dysthymic disorder. As shown in table 1, studies addressing depressed mood as a symptom, either alone or in contrast to other features, predominate (10-12, 15-16, 19-23, 25, 28).

Depressed mood. The frequency of depressed mood in patients with Alzheimer's disease ranged from 0% to 87% in these reports (median=41%), with the modal frequencies most commonly between 40% and 50%. Higher frequencies (42%-55%) tended to occur in samples drawn from psychiatric wards or clinics associated with acute care (general hospital) settings (16, 19, 20, 22). An exception was an investigation that derived its data from semistructured interviews with the families and caregivers of outpatients residing in the community (28). The authors of that study attributed the highest reported frequency of depressed mood (87%, based on the description of "dysphoria" in the *DSM-III* criteria for major depressive episode)

TABLE 1. Affective Symptoms of Patients With Alzheimer's Disease in 18 Studies^a

Study	Sample Size		Facility, Data Source	Mood		Method of Diagnosis	
	AD	Control Group ^b		Depressed	Elevated	AD	Mood Symptoms, Disorders
Rothschild (15)	31	29	State psychiatric hospital, charts	—	AD: 1/31 (3%)	Pathology	Clinical
Sim & Sussman (16)	22	24	General hospital psychiatry ward, patients	MID: 4/29 (14%) AD: 12/22 (55%) OD: 11/24 (46%)	— AD: 1/22 (5%) OD: 4/24 (17%)	Pathology	Clinical
Rosenstock (17)	11	0	VA hospital (? neurology/psychiatry), charts	4/11 (36%) ^{c,d}	—	Clinical	Clinical
Birkett (18)	10	14	State psychiatric hospital, patients	1/10 (10%) ^{c,e}	—	Pathology	Own scale
Nott & Fleminger (19)	15	20	General hospital psychiatry clinic; patients, charts	AD: 7/15 (47%) OD: 3/20 (15%)	— —	Clinical	Clinical
Liston (20)	46	4	General hospital psychiatry ward, charts	Ever: 23/50 (46%) At onset: 15/50 (30%) At diagnosis: 8/50 (16%)	— — —	Clinical	Clinical
Ron et al. (21)	33	0	Psychiatric hospitals; patients, charts	30%	—	Clinical	Clinical
Ballinger et al. (22)	77	23	General hospital geropsychiatry ward, patients	42% Depressive thoughts: 11% 17/85 (20%) ^c	8% —	Clinical	Goldberg interview
Reifler et al. (13)	60	25	Geriatric outpatient clinic, patients	—	—	DSM-III	RDC
Bucht & Adolfsson (23)	18	20	Dementia research group, patients	AD: 11% MID: 0%	AD: 17% MID: 5%	Clinical	CPRS
Knesevich et al. (11)	30	30 ^f	Longitudinal memory and aging project, patients	AD: 0% NC: 0%	— —	Clinical	Hamilton, Zung scales
Kral (24)	40	0	Psychiatric hospital geriatric unit, charts	6/40 (15%) ^c	—	Clinical	Clinical
Rosen et al. (25)	27	28 ^f	VA hospital psychiatry service, patients	— ^g	—	Clinical	Own scale
Berrios (26)	74	26	Geropsychiatry referrals, patients	—	AD: 10/74 (14%) OD: 1/26 (4%)	Clinical	Clinical
Reding et al. (27)	99	57	Dementia clinic, patients	AD: 19% ^c OD: 9% ^c	— —	Clinical	DSM-III
Cummings et al. (10)	30	15	Neurobehavioral referrals, patients	AD: 5/30 (17%) MID: 9/15 (60%) AD: 0/30 (0%) ^c MID: 4/15 (27%) ^c	— — — —	DSM-III	DSM-III, Hamilton scale
Lazarus et al. (12)	44	42 ^f	AD research project, patients	AD: 40% NC: 12%	— —	Clinical	Hamilton scale
Merriam et al. (28)	175	0	Outpatient neurology center, patients	152/175 (87%) 150/175 (86%) ^c	— —	DSM-III	DSM-III

^aAD=Alzheimer's disease; OD=other dementias; NC=normal control subjects; MID=multi-infarct dementia; CPRS=Comprehensive Psychopathological Rating Scale; RDC=Research Diagnostic Criteria.

^bControl group consisted of patients with OD unless normal control subjects are specified.

^cDepression as disorder (see text).

^dOne bipolar, three unipolar depressed.

^eBipolar.

^fNormal control subjects.

^gNo significant difference in depressed mood between groups, but frequencies not stated; tearfulness significantly greater in AD ($p<0.045$).

to the improved ascertainment that resulted from using data from ancillary sources. However, they acknowledged that the unusually high frequency they observed may have been an overestimate of the prevalence of this symptom. In general, lower frequencies (0%—

17%) of depressed mood were noted among dementia clinic outpatients and research subjects (10, 11, 23). It is possible that these groups constitute a more representative at-risk sample. Across studies, observed differences in frequency were not related to whether

symptoms were determined by subjective patient report and/or caregiver report, by clinician assessment, or by depression rating scales, although direct comparison of these different methods of assessment has not been reported.

Few studies compared the frequency of depressed mood in Alzheimer patients with that in normal elderly control subjects. Lazarus et al. (12) found depressed mood in 40% of their patients with Alzheimer's disease and in 12% of the normal control subjects. Two other studies that directly compared Alzheimer's disease patients and normal control subjects failed to demonstrate a significant difference in frequency. In one prospective study (11) that assessed depressed mood longitudinally by both the Hamilton Rating Scale for Depression and the Zung Depression Scale, no one in either group was depressed, which may not be representative. In the other study (25), no absolute frequencies were cited; thus, there was no basis for further evaluation.

Four studies compared the frequency of depressed mood in Alzheimer patients with that in patients with other dementias. In three, depressed mood, measured by clinician assessment, was more common in the Alzheimer patients. The fourth study (10), which measured depression by the Hamilton scale, found the reverse. In this instance, the method of assessment may have been a primary variable contributing to different outcomes. However, it was not always clear which diagnoses constituted "other dementias"; hence, the potential for diagnostic misclassification or the possibility of dissimilar comparison groups among these studies may at least partially account for the differences in results.

Depressive disorders. When depression was identified in the context of specific disorders (major depression, bipolar disorder, dysthymic disorder) and not as isolated mood disturbance, reported frequencies in Alzheimer's disease ranged from 0% to 86% (median = 19%), with most frequencies clustered between 10% and 20% (13, 18, 24, 27). The lower frequencies appeared to be a consequence of the more restrictive and consistent criteria required to diagnose a specific affective disorder. Again, an exception is the report in which data were derived from interviews with families and caregivers (28).

Only two studies compared the frequency of depression as a disorder in Alzheimer's disease with that in other dementias. One study (27) found depression to be more common in Alzheimer's disease, while the other (10) reported the opposite. Although both studies included dementia patients referred for outpatient care, the sample that exhibited a lower frequency of depressive disorders in Alzheimer patients was composed predominantly of inpatients referred for neuro-behavioral problems. Furthermore, this study compared Alzheimer patients to multi-infarct dementia patients only, rather than to a heterogeneous group of dementia patients. Thus, differences in the frequency

of depression as a disorder may have been mainly attributable to differences in the study samples.

Elevated mood. In contrast to depressed mood or disorder, elevated mood seems to occur with consistently low frequency in Alzheimer's disease. The studies reported frequencies ranging from 3% to 17% (15, 16, 22, 23, 26). Two (23, 26) of three studies that compared Alzheimer patients and patients with other dementias found elevated mood to be more common in Alzheimer's disease than in other dementias. Comparison data from the normal elderly population on this isolated symptom are not available. Similarly, although Alzheimer patients with bipolar disorder who manifest predominantly depressive episodes have been described (18, 19), to our knowledge, none with exclusively manic episodes have been reported.

Summary. Affective disturbance appeared to affect a sizable minority of the Alzheimer's disease patients at some time during the course of the disorder. Depressed mood alone occurred most frequently (40%–50%), whereas actual depressive disorders (10%–20%) and elevated mood were less common. For a given problem, variation in frequency seemed most related to differences in the study samples, especially source of patients and treatment setting, as well as to heterogeneity within each diagnostic group. Assessment based primarily on subjective reports by patients and/or caregivers may possibly have overestimated frequency, whereas clinician assessment and depression rating scales appeared to yield comparable results. (However, determining the optimal methods for assessing mood in Alzheimer's disease patients will require direct comparison in future studies.) Although the data are equivocal, both depressed mood and depressive disorders appear to be more frequent in Alzheimer's disease patients than in normal elderly control subjects or heterogeneous groups of dementia patients in many studies.

Psychotic Symptoms

Evaluation of psychotic symptoms in Alzheimer's disease has been complicated by the past convention of referring to dementias, including Alzheimer's disease, as "senile psychoses." Consequently, in some early studies, psychotic symptoms in Alzheimer's disease were not always distinguished from cognitive symptoms and their behavioral concomitants. Even in recent studies, psychotic symptoms have variously been reported as specific delusions or hallucinations or in less readily categorizable forms (e.g., bizarre behavior, unusual delusions or hallucinations, or "psychosis") (table 2).

Delusions. When specific delusions were considered, persecutory delusions were the most commonly described psychotic symptoms. Although reported frequencies of Alzheimer patients who had experienced delusions at some time in the course of their illness ranged from 10% to 73%, the greatest number of studies had clusters between 30% and 38% (median = 33.5%). These investigations (10, 17, 22, 37) reflected

TABLE 2. Psychotic Symptoms of Patients With Alzheimer's Disease In 21 Studies^a

Study	Sample Size		Facility, Data Source	Psychotic Symptoms			Method of Diagnosis	
	AD	Control Group ^b		Delusions ^c	Hallucinations	Not Otherwise Specified ^d	AD	Psychotic Symptoms
Rothschild (15)	31	29	State psychiatric hospital, charts	AD: 7/31 (23%)	—	—	Pathology	Clinical
Goodman (29)	23	0	State psychiatric hospital, charts	"Common"	AH: 3/23 (13%) VH: 5/23 (22%)	—	Pathology	Clinical
Sim & Sussman (16)	22	24	General hospital psychiatry ward, patients	—	—	AD: 7/22 (32%)	Pathology	Clinical
Rosenstock (17)	11	0	VA hospital (? neurology/psychiatry), charts	4/11 (36%)	—	4/11 (36%)	Clinical	Clinical
Birkett (18)	10	14	State psychiatric hospital, patients	1/10 (10%)	—	4/10 (40%)	Pathology	Own scale
Coblentz et al. (30)	20	10	General hospital neurology service, patients	—	—	AD: 2/10 (20%) OD: 5/10 (50%)	Clinical, pathology	Clinical
Liston (20)	46	4	General hospital psychiatry ward, charts	—	—	Ever: 16/50 (32%) At onset: 7/50 (14%) At diagnosis: 2/50 (4%)	Clinical	Clinical
Ballinger et al. (22)	77	23	General hospital geropsychiatry ward, patients	38%	34%	—	Clinical	Goldberg interview
Rabins et al. (6)	33	22	General hospital psychiatry service, caregivers	23/49 (47%)	24/49 (49%)	—	DSM-III	Clinical
Berrios & Brook (31)	72	76	Geropsychiatry referrals, patients	—	—	AD: 19/72 (26%) OD: 25/53 (47%) — ^f	Clinical	Clinical
Rosen et al. (25)	27	28 ^e	VA hospital psychiatry service, patients	—	—	—	Clinical	Own scale
Berrios (26)	74	26	Geropsychiatry referrals, patients	—	AD: 21/74 (28%) OD: 7/26 (27%)	26/74 (35%) 9/26 (35%)	Clinical	Clinical
Berrios & Brook (32)	68	34	Geropsychiatry referrals, patients	—	—	AD: 23/68 (34%) OD: 9/26 (35%)	Clinical	Clinical
Cummings (9)	27	0	Neurobehavioral referrals, patients	4/27 (15%)	—	—	DSM-III	Clinical
Leuchter & Spar (33)	14	15	General hospital psychiatry ward, geriatric unit; charts, patients	22/30 (73%)	AH: 10/30 (33%) VH: 8/30 (27%)	—	DSM-III	IPSC-E
Mayeux et al. (34)	138	0	General hospital neurology service; charts, patients	—	—	50/138 (36%)	DSM-III	BPRS
Mayeux et al. (35)	121	0	General hospital neurology service; charts, patients	—	—	46/121 (38%) ^g	DSM-III	BPRS
Jorgensen & Monk-Jorgensen (36)	9	10	Community psychiatric clinic, charts	10/19 (53%)	—	11/19 (58%) ^h	Clinical	Clinical
Cummings et al. (10)	30	15	Neurobehavioral referrals, patients	AD: 9/30 (30%) ⁱ MID: 6/15 (40%) ⁱ	AH: 1/30 (3%) VH: 0/30 (0%) AH: 2/15 (13%) VH: 3/15 (20%)	— — — —	DSM-III	Clinical

TABLE 2 (continued)

Study	Sample Size		Facility, Data Source	Psychotic Symptoms			Method of Diagnosis	
	AD	Control Group ^b		Delusions ^c	Hallucinations	Not Otherwise Specified ^d	AD	Psychotic Symptoms
Merriam et al. (28)	175	0	Outpatient neurology center; patients, caregivers	56%	28%	—	DSM-III	SADS-C
Teri et al. (14)	127	0	Outpatient geriatric clinic, patients	24%	21%	—	DSM-III	Clinical
Rubin et al. (37)	110	0	Alzheimer Disease Research Center outpatients	31%	AH: 10% VH: 15%	23% ⁱ 4% ^k	Clinical	Clinical

^aAD=Alzheimer's disease; OD=other dementias; AH=auditory hallucinations; VH=visual hallucinations; MID=multi-infarct dementia; IPSC-E=Inventory of Psychic and Somatic Complaints, Elderly.

^bControl group consisted of patients with OD unless normal control subjects are specified.

^cDelusions in general or paranoid delusions; other specific forms of delusions classified as not otherwise specified.

^dIncludes unspecified psychotic symptoms, specific delusions other than paranoid, and hallucinations other than auditory or visual.

^eNormal control subjects.

^fNo significant difference from normal elderly control subjects; frequencies not stated.

^gFrequency varied by subgroup (see text).

^hOther forms of delusions.

ⁱCurrent symptoms; past delusions in AD: 5/30 (17%), in MID: 1/15 (7%).

^jMisidentifications.

^kWell-systematized delusions.

a variety of research strategies and settings (see table 2). Higher frequencies occurred in studies with a selective focus on delusions in heterogeneous elderly patient groups (33, 36). In these studies, prevalence may have been overestimated by reporting the proportion of patients *with Alzheimer's disease* in their samples (delusional patients) rather than the proportion of patients *with delusions* in groups of Alzheimer or other demented patients. The lowest frequency occurred in a study that identified persecutory delusions only in the more restrictive diagnostic context of "paraphrenia" (18).

In a well-controlled study, Cummings et al. (10) directly compared the frequency of persecutory delusions in Alzheimer's disease with that in multi-infarct dementia. Persecutory delusions were noted in 30% of the patients with Alzheimer's disease and in 40% of the patients with multi-infarct dementia. Interestingly, when past delusions were compared in these groups, persecutory delusions had occurred more frequently in the Alzheimer's disease patients (17%) than in the patients with multi-infarct dementia (7%). The fact that the Alzheimer patients were significantly more impaired cognitively at the time of study than were the patients with multi-infarct dementia may account, in part, for this disparity. Comparison data for the frequency of delusions in the nondemented elderly population are unavailable.

Hallucinations. The reports suggested that hallucinations of any type occurred only slightly less frequently than other psychotic symptoms in Alzheimer's disease (median=28%, range=21%–49%). Higher frequencies of hallucinations were observed in patients in acute care (general hospital) settings, whereas lower frequencies were seen in patients referred for outpa-

tient care. It is impossible to determine from these studies whether this disparity in frequency reflects misidentification of coexisting delirium in hospitalized patients, underreporting by outpatients, or some combination of these or other factors. When the specific form of hallucinations was considered, visual hallucinations occurred somewhat more often (median=22%) than did auditory hallucinations (median=13%) in Alzheimer's disease patients.

One study that directly compared the frequency of hallucinations in Alzheimer's disease with that in other dementias (26) found the frequencies to be essentially the same (28% and 27%, respectively). However, Cummings et al. (10), comparing the frequency of hallucinations in Alzheimer's disease and in multi-infarct dementia, found that both auditory and visual hallucinations were more common in multi-infarct dementia (auditory hallucinations, 3% and 13%; visual hallucinations, 0% and 20%, respectively). Berrios (26) studied patients with a specific clinical syndrome, of which Alzheimer patients were only a fraction, whereas Cummings et al. (10) studied Alzheimer and multi-infarct dementia patients; this may explain the difference in outcomes.

Psychotic symptoms not otherwise specified. Psychotic symptoms that were consistently described but difficult to categorize were reported some time during the course of Alzheimer's disease in 20%–58% of the patients (median=34.5%). As with specified delusions, frequencies clustered between 30% and 40% in eight of the 12 studies that reported such symptoms (16–18, 20, 26, 32, 34, 35). Similarly, the higher frequency noted in a study of psychotic symptoms (36) in a heterogeneous group of elderly patients, rather than specifically in Alzheimer or other demented patients, may

have overestimated the occurrence. Although there is still reasonable debate about whether such symptoms are truly psychotic or are the consequence of severe confusion per se, Rubin et al. (37) argued that, particularly for misidentification of people or images, bizarre behavior associated with unusual cognitive or perceptual events justifies inclusion of these phenomena as psychotic.

Several investigators compared the frequency of psychotic symptoms not otherwise specified in Alzheimer's disease with that in other dementias. Berrios and Brook (31), in studies of psychopathology in heterogeneous groups of elderly patients, and Coblenz et al. (30), in a clinical analysis of CSF dynamics in presenile dementia patients, found such symptoms to be more common in patients with other dementias. However, the absolute frequencies of psychotic symptoms for both of these patient groups were lower (20%–26%) than those in most other reports, suggesting that these studies may not have been representative. Interestingly, in two other studies (26, 32), Berrios's group reported essentially equal frequencies of psychotic symptoms in Alzheimer's disease and in other dementias.

Summary. Psychotic symptoms in some form have been generally reported to affect approximately one-third of Alzheimer's disease patients at some time, although a broad range of frequencies has been observed. Disparities in observed frequencies may be attributable to different primary research questions and strategies (especially selection of patient samples) among the studies, although results of methodologically stronger and weaker investigations overlap considerably. Delusions—particularly, simple, persecutory delusions—were the most commonly observed psychotic symptoms, occurring at a median frequency of 34%. Hallucinations and psychotic symptoms not otherwise specified were noted with similar, although slightly lower, frequency. The evidence is equivocal about whether the frequency of psychotic symptoms in Alzheimer's disease differs from that observed in other dementias.

Associated Factors

Although female gender and past or family psychiatric history have been implicated as risk factors for Alzheimer's disease itself, no studies addressed whether these factors specifically predispose to developing affective or psychotic symptoms in Alzheimer's disease. Similarly, several studies suggested that both visual and auditory impairment were more common in psychotic elderly patients, with and without dementia (10, 26, 31, 33). However, neither the presence of nor the type of sensory impairment distinguished psychotic Alzheimer patients from other patient groups (33). Therefore, the precise relationship of sensory impairment to psychotic symptoms in Alzheimer's disease has not been clarified.

One issue is whether specific clinical subtypes of Alzheimer's disease are associated with affective or psy-

chotic symptoms. Mayeux et al. (35) reported four clinical subtypes differing in degree of cognitive impairment, rate of cognitive decline, neurologic symptoms, and psychiatric symptoms. On initial evaluation, patients with extrapyramidal symptoms had psychotic symptoms twice as frequently (50% versus 26.6%) as patients without extrapyramidal symptoms. When drug-induced extrapyramidal symptoms were considered separately, the frequency of psychotic symptoms was three times that of those who were unaffected. Patients with extrapyramidal symptoms or drug-induced extrapyramidal symptoms had greater cognitive impairment than those without these symptoms (mean modified Mini-Mental State scores were 21.7, 10.4, and 30.5, respectively). A similar pattern was observed for patients with myoclonus: the initial frequency of psychotic symptoms was higher (45% versus 37%) and cognitive impairment was greater (mean modified Mini-Mental State scores=16.2 versus 26.9) than for patients without myoclonus. The authors suggested that subgroups of patients with extrapyramidal symptoms or myoclonus, psychosis, and more pronounced cognitive impairment may have a more generalized form of Alzheimer's disease with more widespread deterioration of neurotransmitter systems than is typically seen (35).

A parallel issue is the relationship of the clinical stage of Alzheimer's disease (i.e., the specific signs and symptoms that characterize the progression of the disease from early to advanced) to the occurrence of psychiatric symptoms. The considerable literature on "depressive pseudodementia" highlights the difficulty of initially distinguishing between depression and dementia. First, there is often an overlap in cognitive and vegetative symptoms between the two conditions. Furthermore, Alzheimer patients, even those with only mild cognitive impairment, may have difficulty accurately describing subjective affective states that may accompany more observable symptoms. Nonetheless, a greater frequency of affective symptoms early in the course of Alzheimer's disease has been inferred. In addition, there is a paucity of specifically validated diagnostic instruments for depressed demented patients. Nevertheless, a growing body of evidence suggests the coexistence of affective and cognitive disturbances in the elderly (38). Several of the studies we reviewed confirmed these observations. Moreover, both Kral (24) and Reifler et al. (13) noted depressive symptoms in a proportion of patients in advanced stages of Alzheimer's disease. To our knowledge, no investigation has addressed the relative frequency of affective symptoms across clinical stages in Alzheimer's disease or their course longitudinally in the disease.

The relationship of psychotic symptoms to the clinical stage of Alzheimer's disease presents a similar problem. Two (16, 30) of three studies reported that psychosis occurred in the later stages of Alzheimer's disease. On the other hand, the study which reported that psychosis occurred early in the course of Alzheimer's disease (29) was performed by investigating

post-mortem diagnoses of patients in a state psychiatric hospital, a design which may have biased the results toward finding an early occurrence of psychosis. Consequently, the data on the relationship of psychotic symptoms to the clinical stage of Alzheimer's disease are equivocal.

Cognitive Function and Psychiatric Symptoms

Despite considerable research emphasis on the cognitive aspects of Alzheimer's disease, few studies have examined the relationship of cognitive function to the occurrence of psychiatric symptoms. One question is whether the occurrence of affective or psychotic symptoms is related to the degree of cognitive dysfunction. This issue runs parallel to the question of clinical stage, of which cognitive impairment is a dramatic and often determining characteristic. Reifler et al. (13) and Merriam et al. (28) directly assessed both the degree of cognitive impairment and the prevalence of depression in Alzheimer's disease. Both groups found depression more frequently in the patients with less severe cognitive impairment. However, Merriam et al. judged this difference to be statistically but not clinically significant in their study.

Six studies addressed the relationship of global cognitive function and psychotic symptoms. Three of these studies (9, 10, 15), although differing widely in objectives and design, suggested that psychotic symptoms—specifically, delusions—were more likely to occur in patients with higher levels of cognitive function. Consequently, Cummings et al. (10) advanced the hypothesis that some degree of cognitive integrity may be necessary to generate and maintain delusions. On the other hand, Teri et al. (14), in a prospective study of recently referred patients with Alzheimer's disease, found no significant difference in the frequency of hallucinations or suspiciousness at different levels of cognitive function. Another investigation of a similar sample reported an association between hallucinations, but not paranoid phenomena, and greater cognitive impairment (28). Finally, Mayeux et al. (34) noted significantly greater cognitive impairment in patients who had displayed psychotic symptoms at some earlier time.

Unfortunately, most of the published studies that have addressed this topic have been cross-sectional or retrospective. Consequently, the exact nature of any association between cognitive impairment and psychotic symptoms in Alzheimer's disease remains ambiguous. Mayeux et al. (34), who retrospectively examined the rate of cognitive decline in Alzheimer patients with psychosis, noted significantly more rapid deterioration in those patients. Therefore, while some reported studies appeared to support an association between less severe cognitive dysfunction and the occurrence of associated psychotic symptoms in Alzheimer's disease, the possibility exists that early occurrence of psychosis defines a subset of patients with a more aggressive course in whom cognitive impairment

and psychotic symptoms are more closely linked. To clarify the problem, additional longitudinal study of the relationship between psychiatric symptoms and the progression of cognitive deficits will be required.

A related question is whether specific patterns of cognitive impairment identify Alzheimer's disease patients with associated affective or psychotic symptoms. Various studies (39–43) have suggested that specific patterns of cognitive impairment reflect corresponding underlying patterns of both structural and functional impairment. For example, Martin et al. (42) reported that in Alzheimer patients a predominance of word-finding deficits or visuoconstructive impairment corresponded to relatively greater left and right temporoparietal glucose hypometabolism, respectively. There is an emerging body of evidence suggesting a similar relationship for various psychiatric symptoms, e.g., a "hypofrontal" pattern of regional blood flow and glucose metabolism exhibited by schizophrenic patients with predominantly negative symptoms (44). If analogous associations of cognitive impairment or psychopathology with specific measures of structural and functional impairment can be demonstrated in Alzheimer's disease, an additional question would be whether the underlying site(s) of dysfunction implied by specific cognitive impairments and specific psychiatric symptoms correspond, thus suggesting a possible unifying mechanism for both types of symptoms.

To our knowledge, no published study has directly examined these questions in Alzheimer's disease. However, in a preliminary investigation of Alzheimer patients, we found a possible association between the presence of delusions and deficits on certain neuropsychological tests. If confirmed, these findings may support the existence of a subset of Alzheimer's disease patients in whom psychotic symptoms are associated with specific patterns of cognitive dysfunction. Examination of the relationship between these findings and findings from advanced brain imaging techniques in the same patients may help to elucidate underlying sites of dysfunction involved in the development of psychotic symptoms.

DISCUSSION

Our review suggests that a substantial proportion of all patients with Alzheimer's disease may experience concomitant psychopathology at some time during the course of their illness. Isolated affective or psychotic symptoms complicate Alzheimer's disease two to three times more frequently than do full-blown psychiatric disorders. Aside from the distinction between isolated symptoms and actual disorders, heterogeneity within diagnostic groups and differences in the source of subjects appear to account for much of the variability among studies. Surprisingly, the use of standardized symptom rating scales rarely seemed to alter the estimates of symptoms obtained by clinical assessment, although no direct comparison was reported; both

types of assessment seemed to produce more conservative estimates than did relying on subjective patient and/or caregiver reports.

Another consistent observation was the tendency of studies conducted in acute care settings to see a greater frequency of psychiatric symptoms in patients with Alzheimer's disease. At least two explanations are possible. First, there may have been more reliable ascertainment of symptoms at these more controlled sites. Alternatively, patients seen in acute care settings may have represented a more severely affected subset in whom psychiatric symptoms were more common. Longitudinal studies that examine the same cohorts in both community and acute care settings may help to distinguish between these possibilities.

There are several potential limitations to the possible conclusions from this review that may reflect the methodological problems noted earlier. Our review strategy retrieved a relatively small number of studies spanning several decades, during which consensus and precision with respect to descriptive phenomenology and diagnostic criteria for both Alzheimer's disease and affective and psychotic psychopathology have evolved. We may have sacrificed some breadth of data for the sake of reviewing somewhat more comparable reports in the hope of achieving interpretable results. Nevertheless, the studies we reviewed varied widely in some respects; however, if our criteria for inclusion had been too strict, we would have had very little to review!

A more critical issue, however, is whether the methodological limitations both of the published studies and of our review strategy allow any reasonable conclusions about psychopathology in Alzheimer's disease. A correct inference may be drawn even from a methodologically flawed study. In that case, it is the strength rather than the validity of the inference that may be compromised. Moreover, any review of published research reports yields to a degree of publication bias (tendency to publish reports with "significant" findings rather than studies with negative findings, however well-executed). In the studies we reviewed, accurate estimates of prevalence and potential associations with demographic or clinical factors may have been obscured by small samples and/or misclassification bias. Furthermore, hypotheses that psychiatric symptoms occur more (or less) frequently in patients with Alzheimer's disease than in patients with other dementias or in an age-comparable nonpatient population have not been adequately tested. Thus, there may be limited generalizability of the published observations.

To enhance both the validity and strength of inferences in future analyses, we suggest that the following recommendations receive particular attention in Alzheimer's disease research.

1. Specific a priori hypotheses related to psychopathology in Alzheimer's disease should be identified and tested in each study.

2. The characteristics of the study sample, particularly the source of patients and the selection proce-

dures, should be clearly reported, so that the representativeness and comparability of cases and control subjects can be established. Larger sample sizes might enhance representativeness.

3. The design should be prospective and longitudinal to facilitate research involving the course of affective and psychotic symptoms as they relate to the course of Alzheimer's disease.

4. Case definition should be standardized by valid criteria, and target symptoms should be assessed by reliable and valid rating instruments.

5. Statistical analysis should be appropriate to the hypotheses and the sample characteristics; for example, subjects should be stratified by relevant secondary criteria, such as inpatient or outpatient status, community or institutional residence, clinical stage or level of cognitive function, past or family psychiatric history, sensory impairment, or potentially confounding medical diagnoses when these have not been criteria for exclusion. This will allow comparison on these features and the possible identification of particular subsets of patients at greater risk.

6. Conclusions that may reasonably be drawn from the study should be clearly reported, implications for the specified a priori hypotheses should be discussed, and hypotheses for further study may then be proposed.

Numerous questions remain about the theoretical and clinical ramifications of affective and psychotic symptoms in Alzheimer's disease. Despite their considerable prevalence, the incidence and precise lifetime risk of affective and psychotic symptoms in Alzheimer's disease are still to be established. Likewise, the precise meaning and mechanisms of psychiatric symptoms in Alzheimer's disease remain undetermined. Because both Alzheimer's disease and isolated psychiatric symptoms are relatively frequent in elderly persons, it is to be expected that these processes, if independent, would be superimposed in some individuals. However, the reported prevalence estimates for both affective and psychotic symptoms in Alzheimer's disease appear to rule out the possibility that this coincidence alone accounts for the observed frequency of psychiatric symptoms in Alzheimer patients.

Several alternative explanations can be proposed. One possibility is that preexisting psychopathology in some way predisposes to the development of Alzheimer's disease. As noted previously, there are insufficient published data to support or refute such a relationship. A further possibility is that psychotic and affective symptoms in Alzheimer's disease can be adequately explained on the basis of cognitive impairment itself. For example, paranoid phenomena in Alzheimer's disease have been explained as an adaptive response to a decreased ability to comprehend reality owing to declining cognitive function (10). Similarly, depressive phenomena have been attributed to reaction to the multiple losses attendant on cognitive deterioration (24). However, one might then expect a more idiosyncratic expression of these symptoms in response to individualized meaning and circumstances, rather

than the consistent phenomenology that was observed across these studies, which makes the explanation that these symptoms are simply misinterpretations arising from cognitive deficits or reactions to cognitive deficits unconvincing. An alternative explanation is that in some Alzheimer patients, affective or psychotic symptoms (or both), rather than occurring coincidentally or in reaction to cognitive deficits, arise as manifestations of a common pathophysiology attributable to Alzheimer's disease itself. This hypothesis requires further direct evaluation. Whether affective and psychotic processes in patients with Alzheimer's disease are distinct from similar processes in patients without Alzheimer's disease is a related question. Similarly, the relationship between concomitant affective and psychotic symptoms in Alzheimer's disease bears examination.

Recent technological advances facilitate specific psychobiological strategies to elucidate these questions. Examination of putative biological correlates (sleep, neuroendocrine and psychopharmacological probes, etc.) of "primary" affective and psychotic processes may help determine whether phenomenologically similar processes in Alzheimer's disease have the same neurobiological substrate. Similarly, advanced brain imaging techniques (magnetic resonance imaging, positron emission tomography, single photon emission computerized tomography), which permit localization of function (i.e., metabolic activity), may enhance an integrated understanding of underlying site(s) of dysfunction and symptom patterns. For example, it would be possible to test whether Alzheimer's disease patients with paranoid symptoms exhibit greater frontotemporal dysfunction, evidenced by neuropsychological patterns and brain imaging, as might be expected from hypothesized sites of psychotic symptom generation.

The preceding strategies focus on patients with Alzheimer's disease only. However, relevant information can also be obtained by studying the risk and phenomenology of Alzheimer's disease and of psychiatric symptoms complicating Alzheimer's disease as these may develop in patients who already have another disorder—psychiatric, medical, or neurologic—of relatively known neurobiology. Similarly, parallel studies of other dementing disorders may clarify the relevance of affective and psychotic symptoms in these conditions and, by comparison, contribute to a like understanding in Alzheimer's disease.

Finally, in addition to tackling the still unanswered theoretical questions, future research must incorporate a clinical focus. Treatment studies of affective and psychotic processes in Alzheimer's disease have been infrequent. At present, published data are insufficient to guide clinical management precisely. However, given that psychiatric symptoms complicate the course of the disease in a substantial percentage of Alzheimer patients, each patient should be examined expressly for depressive or psychotic symptoms. When such symptoms are identified, clinicians should also consider the impact of these symptoms on the patient and the caregiver, as well as how much benefit may be gained

from treatment of potentially reversible symptoms. These issues are important because they are often practical determinants of the quality of life for patients and their families. Since discussion of specific treatment options is beyond the scope of this paper, we refer the reader to a recent review (45).

As the proportion of the population at risk for Alzheimer's disease increases, the number of individuals with psychiatric complications of the disease will grow. The challenge of integrating theoretical knowledge about disease nosology, mechanisms, and biopsychosocial correlates into a conceptual framework to meet this emerging clinical exigency will be of interest to general psychiatrists and investigators alike.

REFERENCES

1. Terry RD, Katzman R: Senile dementia of the Alzheimer's type. *Ann Neurol* 1983; 14:497-506
2. Alzheimer A: Über eine eigenartige Erkrankung der Hirnrinde. *Allemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin* 1907; 64:146-148
3. Wells CE: Organic syndromes: dementia, in *Comprehensive Textbook of Psychiatry*, 4th ed, vol 1. Edited by Kaplan HI, Sadock BJ. Baltimore, Williams & Wilkins, 1985
4. Katzman R: Alzheimer's disease. *N Engl J Med* 1986; 314:964-973
5. McKhann G, Drachman D, Folstein M, et al: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group. *Neurology* 1984; 34:939-944
6. Rabins PV, Mace NL, Lucas MJ: The impact of dementia on the family. *JAMA* 1982; 248:333-335
7. Shulman E, Steinberg G: Emotional reactions of Alzheimer's caregivers in support group settings (abstract). *Gerontologist* 1984; 24:158
8. Ferris SH, Steinberg G, Shulman E, et al: Institutionalization of Alzheimer's patients: reducing precipitating factors through family counseling. *Archives of the Foundation of Thanatology* 1985; 12:7
9. Cummings JL: Organic delusions: phenomenology, anatomical correlations, and review. *Br J Psychiatry* 1985; 146:184-197
10. Cummings JL, Miller B, Hill MA, et al: Neuropsychiatric aspects of multi-infarct dementia and dementia of the Alzheimer type. *Arch Neurol* 1987; 44:389-393
11. Knesevich JW, Martin RL, Berg L, et al: Preliminary report on affective symptoms in the early stages of senile dementia of the Alzheimer type. *Am J Psychiatry* 1983; 140:233-235
12. Lazarus LW, Newton N, Cohler B, et al: Frequency and presentation of depressive symptoms in patients with primary degenerative dementia. *Am J Psychiatry* 1987; 144:41-45
13. Reifler BV, Larson E, Hanley R: Coexistence of cognitive impairment and depression in geriatric outpatients. *Am J Psychiatry* 1982; 139:623-626
14. Teri L, Larson EB, Reifler BV: Behavioral disturbance in dementia of the Alzheimer's type. *J Am Geriatr Soc* 1988; 36:1-6
15. Rothschild D: The clinical differentiation of senile and arteriosclerotic psychoses. *Am J Psychiatry* 1941; 98:324-333
16. Sim M, Sussman I: Alzheimer's disease: its natural history and differential diagnosis. *J Nerv Ment Dis* 1962; 135:489-499
17. Rosenstock HA: Alzheimer's presenile dementia. *Dis Nerv Syst* 1970; 31:826-829
18. Birkett DP: The psychiatric differentiation of senility and arteriosclerosis. *Br J Psychiatry* 1972; 120:321-325
19. Nott PN, Fleminger JJ: Presenile dementia: the difficulties of early diagnosis. *Acta Psychiatr Scand* 1975; 51:210-217
20. Liston EH: Clinical findings in presenile dementia. *J Nerv Ment Dis* 1979; 167:337-342
21. Ron MA, Toone BK, Garralda ME, et al: Diagnostic accuracy in presenile dementia. *Br J Psychiatry* 1979; 134:161-168

22. Ballinger BR, Reid AH, Heather BB: Cluster analysis of symptoms in elderly demented patients. *Br J Psychiatry* 1982; 140: 257-262
23. Bucht G, Adolfsson R: The comprehensive psychopathological rating scale in patients with dementia of the Alzheimer type and multi-infarct dementia. *Acta Psychiatr Scand* 1983; 68:263-270
24. Kral VA: The relationship between senile dementia (Alzheimer type) and depression. *Can J Psychiatry* 1983; 28:304-306
25. Rosen WG, Mohs RC, Davis KL: A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984; 141:1356-1364
26. Berrios GE: Presbyophrenia: clinical aspects. *Br J Psychiatry* 1985; 147:76-79
27. Reding M, Haycox J, Blass J: Depression in patients referred to a dementia clinic. *Arch Neurol* 1985; 42:894-896
28. Merriam AE, Aronson MK, Gaston P, et al: The psychiatric symptoms of Alzheimer's disease. *J Am Geriatr Soc* 1988; 36:7-12
29. Goodman L: Alzheimer's disease. *J Nerv Ment Dis* 1953; 117: 97-130
30. Coblenz JM, Mattis S, Zingesser LH, et al: Presenile dementia. *Arch Neurol* 1973; 29:299-308
31. Berrios GE, Brook P: Visual hallucinations and sensory delusions in the elderly. *Br J Psychiatry* 1984; 144:662-664
32. Berrios GE, Brook P: Delusions and the psychopathology of the elderly with dementia. *Acta Psychiatr Scand* 1985; 72:296-301
33. Leuchter AF, Spar JE: The late-onset psychoses. *J Nerv Ment Dis* 1985; 173:488-494
34. Mayeux R, Stern Y, Sano M: Psychosis in patients with dementia of the Alzheimer's type (abstract). *Ann Neurol* 1985; 18:144
35. Mayeux R, Stern Y, Spanton S: Heterogeneity in dementia of the Alzheimer type: evidence of subgroups. *Neurology* 1985; 35:453-461
36. Jorgensen P, Monk-Jorgensen P: Patients with delusions in a community psychiatric service. *Acta Psychiatr Scand* 1986; 73: 191-195
37. Rubin EH, Drevets WC, Burke WJ: The nature of psychotic symptoms in senile dementia of the Alzheimer type. *J Geriatric Psychiatry Neurol* 1988; 1:16-20
38. Reifler BV: Mixed cognitive-affective disturbances in the elderly: a new classification. *J Clin Psychiatry* 1986; 47:354-356
39. Cutler NR, Haxby JV, Duara R, et al: Clinical history, brain metabolism, and neuropsychological function in Alzheimer's disease. *Ann Neurol* 1985; 18:298-305
40. Haxby JV, Rapoport SI: Abnormalities of regional brain metabolism in Alzheimer's disease and their relation to functional impairment. *Prog Neuropsychopharmacol Biol Psychiatry* 1986; 10:427-438
41. Margolin RA, Ban TA: Neuroimaging and psychopharmacology in the diagnosis and treatment of dementia. *Prog Neuropsychopharmacol Biol Psychiatry* 1986; 10:493-500
42. Martin A, Brouwers P, Lalonde F, et al: Towards a behavioral typology of Alzheimer's patients. *J Clin Exp Neuropsychol* 1986; 8:594-610
43. Swigar ME, Benes FM, Rothman SL, et al: Behavioral correlates of computed tomographic (CT) scan changes in older psychiatric patients. *J Am Geriatr Soc* 1985; 33:96-103
44. Buchsbaum MS, Ingvar DH: New visions of the schizophrenic's brain: regional differences in electrophysiology, blood flow, and cerebral glucose use, in *Schizophrenia as a Brain Disease*. Edited by Henn FA, Nasrallah HA. New York, Oxford University Press, 1982
45. Wragg RE, Jeste DV: Neuroleptics and alternative treatments: management of behavioral symptoms and psychosis in Alzheimer's disease and related conditions. *Psychiatr Clin North Am* 1988; 11:195-213

An Ethnomedical Perspective of Anglo-American Psychiatry

Horacio Fabrega, Jr., M.D.

Although psychiatry is part of Western biomedicine and its roots in neurobiology are widely appreciated, Anglo-American psychiatry addresses social behavior that is deviant and potentially stigmatizing and is said to uniquely engage in social control. Moreover, its concerns overlap and compete with those of other regulatory institutions of the state. For these reasons, the manner in which psychiatry operates is subject to challenge, criticism, and controversy. The author proposes that a look at psychiatry from the vantage point of ethnomedicine—the comparative study of medical systems—can enhance an appreciation of the current controversies in psychiatry and psychiatry's role as a medical institution.

(Am J Psychiatry 1989; 146:588–596)

Ethnomedicine is the study of how illness problems are realized and dealt with in different societies (1–4). Emphasis is given to social and cultural factors (5, 6). A fundamental property of ethnomedicine is that it is comparative. The beliefs, attitudes, and actions surrounding illness and healing and the relation of these to symbolic themes in the society have been a dominating focus. Small-scaled societies have usually been the object of study. However, an ethnomedical rationale can and has been used to study complex societies. In such societies, historical and sociological factors that affect the structure, organization, and political economic foundations of medical institutions must also be considered. A basic requirement is that emphasis be given to “ethno” phenomena, namely, what is ordinarily meant by ethos, culture, and symbolic systems. Another requirement is that knowledge drawn from comparative studies of medicine be used to inform the study in an important way.

Research in ethnomedicine shows that all people experience illness and that all societies have practitioners or healers who treat them using accumulated knowledge and traditions (1–4, 7, 8). Ethnomedical

scientists analyze illness as a behavioral and symbolic entity that is not valued and requires corrective action. Cultural conventions about well-being and social function are used as norms to establish that someone is ill (7). The knowledge of illness and medical treatment is an important element of the culture of a society. Ethnomedical concepts of wide applicability are used to describe and explain how medical problems are handled in a society (9, 10). They cover many topics, such as the objects of concern (e.g., illness, disease), conceptualizations about them (e.g., explanatory models, theories of illness), the values and meanings surrounding illness and how these develop and are manifest (e.g., semantic networks of illness, production of medical knowledge, idioms of distress), the persons who treat illness (e.g., practitioners, shamans), and the social practices and institutions that embrace all of these (e.g., medical system, social relations of sickness, the professional sector). Some of these concepts can be used to study biomedicine as a system of medicine and, especially, psychiatry as a component of it.

AN ETHNOMEDICAL LOOK AT ANGLO-AMERICAN ILLNESS

Medicine in contemporary Anglo-American society is dominated by the biomedical theory of illness (7). Moreover, governments certify this theory in that state agencies support, supervise, and regulate its refinement and implementation rather than lay theories of illness. The production of medical knowledge in our society has yielded a distinctive cultural reality to illness: the real or possible existence of an underlying state of disease (disordered physical-chemical or physiological systems) is all important. As a feature of secularization, the technology of biomedical engineering renders the social relations of sickness and treatment in the professional sector impersonal and bureaucratic, yet clothed in the traditions of healing and caring, the ethnomedical verities of medical practice (11–15).

In Anglo-American medicine, to diagnose, to prescribe treatment, and to elicit cooperation in a medical regimen are to ally with the person ill and to conduct a dialogue with him or her about the disease. Aspects of the self are implicated in this dialogue, since cooperation is required and references and procedures are directed at the person's physical traits. It is clear, moreover, that decisions of nonpsychiatric physicians carry

Received Feb. 2, 1988; revision received June 28, 1988; accepted Aug. 5, 1988. From the Department of Psychiatry and Anthropology, University of Pittsburgh School of Medicine. Address reprint requests to Dr. Fabrega, Department of Psychiatry and Anthropology, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213-2593.

Copyright © 1989 American Psychiatric Association.

social control functions (e.g., decisions involving the determination of disability) and that social policies related to diagnosis can lead to the abrogation of civil liberties (e.g., quarantine). Medical labels, thus, have social, political, and moral implications (i.e., medicalization) (16). However, on the whole, medical diagnosis does not logically implicate the self and behavior but, rather, focuses on abstracted parts or systems of the body. Moreover, unlike the practices of psychiatrists, the practices of general physicians do not usually involve them in personal inquiries about the self and its social adjustment or in deliberations of agencies and institutions of the state.

AN ETHNOMEDICAL LOOK AT PSYCHIATRIC ILLNESS

Explanatory models, illness theories, and the semantics of illness are different in Anglo-American psychiatry than they are in the rest of Anglo-American medicine (7, 17, 18). Disease is a more problematic entity. Research involving the genetics, neurochemistry, neurophysiology, and neuropsychology of schizophrenia and disturbances of mood, for example, attests to the importance of disease. However, it is not yet possible to diagnose psychiatric disease by using purely technical procedures or to specify precisely which disease mechanisms accurately account for specific illness configurations. Moreover, there are diagnostic categories for which no disease candidates appear immediately forthcoming (somatoform, dissociative, and psychosexual disorders, for example). If the "brain lesions" of "traditional" disorders are poorly understood and the factors that set them awry are unclear, the putative cerebral disease mechanisms of such disorders can be described as nebulous and it is arguable whether the explanatory models of biomedicine are appropriate.

In psychiatry, definitions of criteria of illness remain anchored in behavior. Although the language of psychopathology is highly secularized and appears to rest on a positivistic framework (19, 20), it cannot be said to refer to impersonal and technical things but to potentially highly personal components of the self, since beliefs, intentions, and modes of thinking and feeling are implicated (21). Psychiatrists' concerns with adjustment to reality and/or social impairment, for example, necessarily plunge them into a consideration of the institutional framework in which individuals exist as moral beings. In short, whereas dialogues about disease in general medicine and surgery are commentaries about the physical body and indirectly about the self, in psychiatry they are direct commentaries on and of the self. Psychiatric diagnosis and treatment, then, necessarily entail a medicalization of social and psychological behavior in a way different from general medicine and surgery. Furthermore, insofar as conventions of diagnosis rest on social and personal norms and diagnostic indicators on deviations from them, psychiatric diagnosis must entail marking social and psycho-

logical (i.e., self) deviance. Finally, since a lack of value and a need to act correctively are intrinsic to the idea of illness, it follows that psychiatric diagnosis and treatment can be personally controlling.

THE SOCIAL "PROBLEMATIQUE" OF ANGLO-AMERICAN PSYCHIATRY

The history of how Anglo-American psychiatry came to have this logical tie to the self and its social ramifications is complex. One part involves the evolution of biomedicine. The beginnings are in the early modern period and involve deliberations of the Royal College of Physicians at the time when biological science was beginning to differentiate from alchemy and astrology. This goes on to the modern era, with developments in the mature sciences that have allowed ever more precise and technical inroads into the body (11-15, 22, 23).

Another part of the history of psychiatry involves the evolution of policies of the modern state related to the care of the mentally ill. This includes, in particular, activities that led to the creation and growth of the asylum. The history of the asylum traces its handling, first of the poor and disabled, then of segregated forms of different types of deviants, and, eventually, of the insane (24-36). Integral to this history is the growth of the profession of psychiatry. Nineteenth-century asylum superintendents ("alienists" and "mad-doctors") were socially empowered to care for increasing numbers of dependent, needy, and mentally ill persons. These superintendents became prominent in a society marked by industrialization, an increasingly dominant market economy, and demographic transitions in the late eighteenth and early nineteenth centuries. The motives and strategies of these "protopsychoanalysts" as well as the bases for their claims and rationale have been critically analyzed in recent years. Nonetheless, the activities of these individuals and their successors led eventually to a sharpening of the science of psychopathology and psychiatric classification. Moreover, their social and political instincts led them to seek a professional identity through accreditation and licensing procedures, thereby creating colleges of medical psychology and psychiatry. This professionalization was instrumental in facilitating and promoting research on the brain.

Viewed ethnomedically, what stands out in this history is the importance of political and economic factors (social policing and rehabilitation, for example), the concomitant, heavy emphases on rationalizing symbols and/or ideologies (involving moral worth and humanitarianism, for example), and the dominance of the state in the way the psychiatrically ill were handled. Implications of these factors for understanding the stigma of psychiatric illness remain to be worked out. We lack information on how the psychiatrically ill were handled in other civilizations. However, we know that in elementary societies they are not dealt

with in any special way compared with others who are ill and dependent. In eighteenth- and nineteenth-century Anglo-American society, however, problems attending the volume and concentration of madness and the real and/or perceived threat that this posed to the state proved influential in the way the psychiatrically ill came to be defined and handled (25–28). This topic is complex and controversial, the object of serious scholarly debate in historical sociology, and central to the criticisms of antipsychiatrists (37). It is not clear if a sharp rise occurred in the number of psychiatrically ill or whether “madness” became more visible and burdensome because of the transformations in society (38, 39). Changes in social structures could have rendered obsolete old familial and communal modes of caring for the mentally ill, resulting in a need for the asylum and institutionalization. Alternatively, changes in structures of the self, coincident with the social changes and contextualized through evolving ideas of individualism and classical liberalism, may have required modes of adaptation that people deemed mad or insane were simply unable to meet (40).

The solution of these problems took on moral and political overtones (41–44). This was inevitable because the solution required control and regulation of dependent and needy people and took place in the context of new ideas involving civil liberties. This was bound to affect those who were the objects of care as well as the caretakers. That psychiatry came to be identified with problems involving the control and regulation of the deviant and marginal clearly set it apart from other medical disciplines, and this association is part of its social tradition. The association is still integral today, mirrored in the semantic network that embraces psychiatric illness and conditions its problems in the medical system and in the society at large (45–50).

What can be termed a social “problematique” thus characterizes the rationale and practice of contemporary Anglo-American psychiatry, which deals with medical phenomena that have moral and political connotations in a society in which medicine has become a quintessentially abstract, impersonal, and secular enterprise. In conceptualizing and dealing with different forms of social deviance, psychiatry strays outside the sphere of its sibling disciplines. Moreover, it can entail a control of the individual and/or an exculpation of his or her actions through a medicalization of the self, and this earns it opprobrium. The totality of these issues has led critical observers to underscore the role of psychiatry in what Kittrie (46) has termed the “therapeutic state.”

The social “problematique” is mirrored in the institutional role that psychiatry plays compared with other medical disciplines. Although its object is still the person in all of his or her behavioral complexity, psychiatry carries out highly visible corporate and institutional functions. As a medical discipline with its own professional association and as a component of society’s medical institutions, it of necessity plays a role

in medical policy. However, in the political economy and structure of modern society, corporate psychiatry becomes involved in the deliberations of other institutions having patent social control functions—in the welfare system, the courtroom, the military, and evaluations for industries, for example. In this arena, what psychiatry stipulates with respect to illness and treatment and how it construes and deals with illness behaviors are geared to the needs of the institution as a regulatory agency. To the extent that individuals’ needs are overlooked or their full citizenship is questioned or suspended, their long-term credibility is injured regardless of any medical and/or social advantages that may accrue in the short run as a consequence of the pursuit of corporate functions.

The clinical-individual and corporate-institutional directives of psychiatry can be inconsistent and occasion conflict and controversy. To address persons in the individualistic mode is to seek their well-being as social and psychological creatures. Here psychiatry is engaged in the time-honored and altruistic pursuit of the medical practitioner-shaman and, given the definition of psychiatric illness as opposed to medical-surgical illness, embraces individuals in their full humanity. Conversely, to address persons in the institutional mode is to potentially thwart, discredit, and/or weaken their full citizenship through psychiatric labeling and, eventually, exculpation and/or control if not coercion. By virtue of promoting goals and pursuits that are opposed and in competition, the conflict in functions can prove burdensome to patients, psychiatrists, and society.

HISTORICAL ANTECEDENTS OF THE SOCIAL “PROBLEMATIQUE”

The social “problematique” of psychiatry has deep historical roots. Social historians have made clear the many social functions that medical practitioners played in early premodern England. In addition to diagnosing and treating illness, including mental illness, they offered advice regarding all sorts of social problems, such as family conflicts, the most propitious times for travel, love and marriage, the whereabouts of lost or stolen property, the suitability of economic ventures, and the identity of witches who perpetrated medical or social evils. Moreover, many practitioners provided spiritual-moral consultations, since they had a theological standing in the community and this was a dominating framework of explanation. The theory of illness prevalent at the time accommodated natural and preternatural agencies of causation. Illness was explained in terms of magic, sorcery, humoral notions, and theology. These seemingly (to the contemporary mind) inconsistent explanatory models were invoked concomitantly in the explanation of illness and judged as additive. Finally, historians have made clear that illness, whether viewed as psychological or physical, was often seen as linked to social and familial happen-

ings of importance and had to be dealt with in an idiom that can be called psychiatric and religious (51–53).

The account of demonic possession and witchcraft during the late sixteenth and early seventeenth centuries in England and Europe provides an excellent illustration of how the clinical, social, and religious functions of “protopsychoiatrists” overlapped and involved institutional functions (54). The overlap of duties was made possible by the theory of illness that prevailed, a theory applied to deviant behaviors that were similar to psychiatric illness. Even at this rather late date, when medical practitioners were already seen as resembling professionals with well-bounded roles and duties, physicians were frequently called on to consult in cases of witchcraft and demonic possession. In the former instance it was often to establish whether an individual displayed physical evidence that reflected her or his status as a witch, although on occasion physicians were asked to comment on the sanity of the person (for example, if delusions were present), which then rendered the witch’s confessions problematic. In the case of demonic possession, physicians’ consultations were sought by civil and religious authorities in the attempt to reach a “differential diagnosis” between illness-related actions and demonic actions. All of these instances provide evidence of how easily the actions and opinions of medical practitioners connoted, entered into, and were deemed as appropriate to the deliberations of representatives of diverse institutions of society. Viewed ethnomedically, the scenarios depicted by this material are clear instances of the conflict between clinical-individual and corporate-institutional functions then characterizing the practice of medicine, which is intrinsic to the social “problematique” of Anglo-American psychiatry today. At this period of Anglo-American history, then, the theory of illness of the professional sector and the semantic network of illness embraced social behavior colored symbolically in terms of religion and the supernatural. Activities within the medical system carried spiritual and legal meanings.

In summary, one historical antecedent of the individual-institutional conflict that is an element of the social “problematique” is rooted in the increasingly public and social role that the medical profession came to play in the society of England in the late sixteenth and early seventeenth centuries. In this setting, the themes of demonology and witchcraft were dominant medical, social, political, and religious concerns and physician “protopsychoiatrists” played prominent roles in helping to resolve them. The developing corporate identity of the profession of medicine had in fact been a dominating feature of English medical practice since late medieval times, and even in this early period the profession was involved in social policy matters as well as in settling issues related to malpractice (55–57). (For concurrent developments in Italy, see references 58 and 59.) Such corporate features of medical practice are not altogether absent even in non-Western peasant societies (60).

Another historical antecedent of the individual-institutional conflict of Anglo-American psychiatry and its social “problematique” involves matters linked to the insanity defense. The social and legal problems that the mentally ill offender poses to the Anglo-American psychiatrist well antedate the establishment of psychiatry as a branch of medicine. Scholars have traced the evolution of legal thinking in this area in the history of the common law (30, 31, 61–68). In order for a rule of precedent regarding the adjudication of an offense to be represented in a legal code the need for it must be perceived and the problem for which the rule constitutes a solution must be common enough to occasion concern, discussion, and formation. Although “the mentally disordered offender raises questions which have troubled theologians, moral philosophers and lawyers throughout the Christian era” (30, p. 6), a slowness characterized the way the criminal law developed in England following the first recorded mention of insane offenders. It was not until 1731 that psychiatry-related testimony was used in a criminal trial, and it was not until 1798 that an accused person was able to call a medical witness during the trial itself. It was in the nineteenth century, of course, that direct attention began to be given to the content and nature of an insane person’s delusions and the extent to which these delusions may have motivated and/or justified or exculpated serious offenses like homicide.

What requires emphasis is the conservatism of the legal institution and its reluctance to accept the idea that psychiatric illness could weaken if not rescind moral and legal culpability for a crime such as homicide. A basic point is that homicide symbolizes the most violent and odious of human acts and, as Foucault (24, 47, 68) has argued, can occasion an equally violent and odious reaction on the part of those whom the homicide affects and in the institutions evolved for its punishment. Perpetrators of homicide who seek understanding and mitigation for their deviance confront a “punishing” state. The nineteenth-century penal reforms, involving a change from torture and the spectacle of the scaffold to what Foucault called “generalized” and “gentle” forms of punishment, are a testimony to the strong aversion to homicide. Both the brutal atrocities to the offender’s body and the controlled and impersonal but pervasive and personally annihilating handling of it in the modern bureaucratic “machinery of the penitentiary” symbolize the enormous quantity of social aggression that is wrought up in the political economy of punishment. These forms of retribution reflect, at a macroscopic level, the personal abhorrence that individuals have of homicide.

In summary, acceptance of the insanity defense has been slow to evolve in Anglo-American society, and controversies surrounding it mirror and symbolize the individual-institutional conflicts of psychiatry and its social “problematique.” Homicide, in effect, embodies a test case of exculpation, the end point of a continuum of social circumstances that the state, its representatives, and its citizenry are able to concede might

possibly erode an individual's sense of responsibility and accountability. In short, it is perhaps the hardest form of deviance for the agencies of social control to neutralize through medicalization.

Two factors that explain the reluctance to accept psychiatric illness as a mitigating factor in the defense are, first, the opprobrium, horror, and odiousness attached to serious crime and, second, the basic difficulty of demarcating illness or insanity from criminal intent and guilt. Homicide, like other crimes, constitutes a social act whose rationale is explainable in terms of motives and intentions that have a readily apparent meaning to social actors. To stipulate that illness is a mitigating factor requires a view of the person as capable of actions that are not willful or motivated in terms of socially motivated ("rational") concerns and a complementary view of illness as anchored in or caused by factors beyond personal control. In essence, mental illness as a defense of homicide requires a suspension of our attribution of personhood if the latter is equated with willful symbolic behavior. Viewed ethnomedically, the difficulty of stipulating the presence of disease, as the biomedical theory of illness requires, is a factor: The logical connection of psychiatric illness with the self. Moreover, it is not clear that a biological marker of homicidal intent could easily be applied, underlining the special connectedness of psychiatric illness with the self and social, moral, and legal phenomena (the semantic network of psychiatric illness).

THE SOCIAL "PROBLEMATIQUE" AND ITS CRITICISMS IN AN ETHNOMEDICAL FRAMEWORK

Social critics of psychiatry stress the inappropriateness of using the positivistic framework of the natural sciences, which are concerned with causality and the behavior of physical objects, to explain human behavior. It is claimed that human behavior involves meaning and symbols and is social and political in nature. In exploiting the positivistic approach, psychiatry is said to regulate and control deviance in the service of the needs of the establishment—the state and its representatives. Ironically, biological determinists, hard exponents of biological psychiatry, help strengthen this critique by narrowly delimiting the domain of psychiatry to exclude much that is social and cultural, as the critics demand.

Another criticism of psychiatry involves its rise as a profession in the nineteenth century. Attention is given to the allegedly self-serving motivations of asylum superintendents, who, despite a relative lack of expertise and success in dealing with insanity, managed to "appropriate" the basic tenets of moral treatment reforms. In conjoining these tenets with prevailing organicist tenets, they "self-servingly" established the medical model of insanity and placed themselves in central positions in the management of lunacy and reform in asylums. Furthermore, the critics assert that with such "false claims," early psychiatrists extended their direc-

tives outside the asylum to the society at large, ultimately instilling their ideas in many other social and welfare institutions concerned with surveillance and control. This, it is said, has led to the creation of the modern "therapeutic state" (46). In this scenario, terms such as "psychiatric imperialism" and "professional entrepreneurship" are used to qualify the alleged self-serving interests of psychiatry (69–71).

An ethnomedical perspective of psychiatric theory and practice qualifies somewhat this critique of psychiatry's theories and practices. Such a perspective shows us that illness, the basic datum of medicine, involves not only social behavior but also deviation from conventional norms. How illness is perceived and resolved in all societies necessarily involves cultural beliefs, values, and actions that are potentially social and political. Moreover, all medical practitioners carry out adjudicatory and mediatory functions. Finally, in some societies (the Ashanti, for example) one finds explicit rules that provide for an exculpation of individual action through an appeal to notions of illness (i.e., criminal actions are judged an outcome of insanity or medical illness) (72). These generalizations are well supported in and integral to ethnomedical knowledge and science and are consistent with fundamental axioms of anthropology. Thus, the social control functions of physicians—especially psychiatrists—are found in a number of different types of societies, not only modern European ones. Similarly, members of all types of societies show a natural inclination to medicalize some forms of deviant behavior. It is only a narrow and reductionistic use of the biomedical theory that deludes us into thinking that medicine is purely a technical and engineering enterprise and that social-psychological aspects of behavior should be the concern of nonmedical personnel.

The rootedness of psychiatry-related activities in ethnomedical verities could be countered by arguing that what happens in "primitive" or nonmodern societies is exotic, romanticized, or simplistic, far removed from the "evolved" and the "scientific." But this is to reason chauvinistically and ethnocentrically. A seemingly stronger argument would stipulate that in elementary societies the prevailing way of accounting for and dealing with deviant actions, including illness, is based purely on moral grounds. That is to say, the essential (or the natural) way in which societies attempt to control and regulate all types of deviant behaviors is by dealing with them socially and politically rather than medically. To deal with them medically, therefore, is not a natural but a secondary, derived, or observer-imposed way of qualifying such behaviors. This argument would emphasize that the idea of a medical system cannot be applied to elementary societies. What one observes instead, the argument would run, is societies in which all behavior, whether medical (by our standards) or deviant, is judged in political and religious or spiritual terms. In other words, phenomena that anthropologists call illness, curing, and related medical activities cannot be equated with phe-

nomena that carry such labels in contemporary Anglo-American society. In simpler societies, such phenomena are simply political and social, and the medical (an allegedly independent domain) cannot be said to exist, much less the idea of illness, medical practitioners, or a system of medical care. The latter terms are appropriately geared to Western civilizations in which a long history, peculiar cultural symbols, and political, economic, and scientific developments endow the phenomena in question with the appropriate meanings.

The preceding argument is weakened by the fact that it can just as well be used with reference to what one means by the political, the legal, or the economic. A controversy in social science, for example, involves whether conflict adjudication and mediation in elementary societies can be equated with law and judges (72). To restrict the meaning of such terms as law, judges, economic self-interest, medical, and curing purely to contemporary Anglo-American societies is to essentially eliminate insights drawn from comparative studies in social science generally and in ethnomedicine in particular.

Critics also emphasize that psychiatric practice is concerned with maintaining the social status quo. They point out that, through diagnosis, human problems rooted in the structure and political economy of the society are inappropriately medicalized. Indeed, according to Ingleby (33, 34), a human distress disorder (for example, depression in an unemployed man) is given a name and thereby reified and then its "objective" manifestations are treated in a neutralized and depoliticized way (rationalized), leaving unexamined the truly social causes of such distress. In other words, the origins of the disease, illness, or maladaptive human response in inconsistencies and conflicts inherent in the social system are not addressed. Instead, it is claimed, the conventions and safe interpretation of the social system are preserved. Probing into its presuppositions, directives, and structures, where the more effective "therapy" should take place, is avoided.

This criticism is weakened by the fact that it inappropriately singles out psychiatry. Social factors are causative of all types of diseases, not just psychiatric ones. Furthermore, why should psychiatry be blamed for pursuing the fruits of its evolved science? Biomedical science is unquestionably impersonal, abstract, and technical, but its theories and the knowledge it produces lead to positive changes in the social system that ameliorate conditions which produce disease. The modern state has other institutions and personnel that use biomedical knowledge explicitly to educate the public and to effect policy changes promoting healthful conditions and behaviors. The power of biomedicine lies precisely in its political neutrality; that is, its ability to deal with phenomena through a language relatively uncluttered and uncontaminated with prevailing social problems and cultural biases. (This in no way vitiates the claim that biomedical tenets are themselves cultural and hence integral to contemporary notions of self, personhood, and social reality.) The processes of

social and cultural evolution have culminated in a "social organ" (biomedicine) efficiently geared to the control and elimination of social and illness problems, and its success is partly an outcome of its relatively asocial and apolitical nature. It is true that medicine can and has expounded misguided and pernicious treatment strategies, but this only emphasizes the need for a prudent regulation of medical practice, not the failures of biomedicine (73). However, to value biomedical science, a cornerstone of contemporary Anglo-American psychiatry, does not mean that the traditional links between psychiatry and the sociocultural should be severed. Nevertheless, the tie that psychiatry has with the self and symbolic behavior places it in a special if socially awkward position.

THE SOCIAL "PROBLEMATIQUE" AND CONTEMPORARY TRENDS

A review of recent trends and developments in social and cultural psychiatry will serve to highlight differing expressions of the social "problematique." This will require a brief review of basic ethnomedical tenets (5, 73-79). An important assumption in any theory of disease is the role played by society in creating disease conditions. This applies to general medicine through a variety of means, such as exposure to toxins, the production of unhealthy work conditions, the provision of unhealthy diets, the creation of social-economic rules and practices that are stressful, and the availability of substances that lend themselves to abuse. Societies can also produce, stabilize, and augment illness conditions by creating circumstances that reinforce illness, be these in the forms of idioms of distress that have interpersonal appeal, modes of directly compensating illness, and/or social rules that indirectly condone, reward, and/or require illness for the attainment of social ends. In many ways societies produce distinctive behavioral styles, both normative and aberrant or "psychiatric." This takes place in a number of ways: through the formation of rules for the regulation and expression of affect, the creation of the symbolic objects that make up one's behavioral environment, and the stipulation of theories pertaining to the self and its functioning. Societies, then, have a hand in the construction of basic categories of psychological functioning. By inculcating values and providing reinforcements relating to physical appearance and social behavior as well as by creating circumstances that reward or punish behaviors related to them, societies have a hand in creating all sorts of personality styles, interpersonal schemes, and social roles. More generally, through the stipulation of social goals, norms, values, ideologies, and appropriate scripts for achieving success, societies create the basic measures of moral, appropriate, and valued behavior. In addition, since opportunity structures are unevenly distributed, societies can facilitate and/or hinder the realization of the goals and needs they themselves inculcate. This can

create conditions for frustrations and behaviors that are not only immoral, not valued, and/or antisocial but also medically and psychiatrically injurious, thus leading to medical intervention.

Anglo-American society may be held to produce socially and psychologically deviant behaviors that are encompassed within contemporary psychiatric theory. As an example, consider the following. 1) Type A behaviors are partly exaggerations of a time-pressured, work-driven capitalistic seeking for maximizing profits. 2) Narcissistic behaviors reflect a pervasive and dominating enmeshment with Anglo-American conventions of appearance and self-sufficiency. 3) Eating disorder behaviors represent internalized runaway conflicts between biological imperatives and conventional valuations of body physique. 4) Depression in divorced mothers represents a natural casualty of a system that provides insufficient support for those attempting to balance competing biological and professional imperatives. 5) So-called borderline disorder behaviors are the outward manifestations of irreconcilable conflicts bearing on women as a result of fundamental changes in feminist psychology and values; studies of social historians and anthropologists (80–84) have documented how cultural stereotypes and biases involving women in Anglo-American society condition psychiatric problems and militate against treatment.

The general point is that societies create 1) goals and objectives for people, 2) symbolizations that connect the goals and objectives to widely prevalent and overdetermined cultural themes and values, and 3) opportunity structures that can facilitate and/or hinder the achievements of these goals and objectives. Social stressors, supporting and/or nonsupporting interpersonal networks that buffer stress, and the social processes that allow people to manage stress are culturally conditioned, as are the behavioral responses that register adaptive failures. In short, the demoralization, misery, disappointments, and frustrations that result from not accomplishing what society itself has determined should be accomplished are clothed in symbolic rubrics that help shape behavior in culturally distinctive ways (85). Clearly, there are behaviors, responses, and/or symptoms that are universal as well as human vulnerabilities that are idiosyncratic. Therefore, human failures could never be said to be fully culturally relative. However, that cultures substantially influence the behavioral experiences of human disturbances and illnesses can hardly be doubted (86). Thus, a contemporary expression of the social "problematique" is illustrated in the way psychiatry capitalizes on casualties of the social system through the creation of illness conditions geared to inversions and negations of symbols having wide appeal in society (84). In other words, the explanatory models of some psychiatric conditions—in some instances their stipulation in the nosology—are geared to politicized and nontestable norms of acceptable adaptive behavior (87).

Johnson (81) and Swartz (82) have used the concept of culture-bound syndromes to draw attention to the

bias and shortsightedness inherent in Anglo-American psychiatry. They indicated that the concept of a culture-bound syndrome is ethnocentrically applied to exotic behavioral reactions observed in distant and contrasting cultures. Such syndromes appear not to conform to the so-called authentic models of syndromes in Anglo-American societies. Culture-bound syndromes in elementary societies may or may not constitute disorders, unusual reactions, or illness conditions; their cultural logic is overlooked in favor of the observer's scientific theory about behavioral mechanisms and psychiatric nosologies. Johnson and Swartz drew attention to cultural biases implicit in positivistic biomedical psychiatry: the myth that its categories and objects are neutral or objective and hence scientific because they can (in some instances) be shown to have a biological core. In other words, many if not all Anglo-American disorders are in reality culture bound to some extent. Many of these Anglo-American culture-bound syndromes involve women, and the analyses of them have drawn heavily from feminist studies.

An additional aspect of the social "problematique," then, involves what one can refer to as the tendency to export illness and disease categories across national boundaries. Practitioners and theorists of psychiatry from developing countries (88–90) have emphasized the hidden biases of contemporary psychiatric nosologies and the inappropriateness of universalizing Western assumptions about human psychology and psychopathology. An example is the International Pilot Study of Schizophrenia (91) through its rigorous stipulation of criteria for diagnosis. Drawing on European and Anglo-American notions of psychopathology, researchers appeared to be fixing the identity or content of this "disorder." A psychiatric epidemiology naturally requires explicit definitions that are abstract and facilitate reliable diagnosis. Moreover, the success of the International Pilot Study of Schizophrenia in identifying illness conditions cross-culturally must be regarded as partially supporting the validity of the conceptualizations. However, a number of theoretical and empirical problems pertaining to psychiatric illness generally and schizophrenia more specifically are rendered inaccessible through use of International Pilot Study of Schizophrenia criteria, as has been discussed elsewhere (40, 92–94). Stated in summary form, this involves the matter of Anglo-American psychiatry's mentalistic bias (and minimization of the somatic), its reliance on highly abstract and static conceptions of illness and consequent neglect of the elaborated processes and meanings attached to altered behaviors that condition how such behaviors are interpreted and dealt with, its gross disregard of its own ethnocentric assumptions and the ethnopsychological theories of other societies, and finally its methodological procedures, which have the effect of enhancing the likelihood of finding Anglo-American features and missing the culturally variable ones (95, 96). A similar tendency toward universalization is evident in the way

other "traditional" psychiatric disorders are determined—depression, for example—but the problem is far more pervasive (97). From the standpoint of the argument developed in this essay, the social "problematique" of Anglo-American psychiatry is embodied in an epidemiologic rationale that fixes the identity of illness. In a sense, the illusion of biomedical neutrality and impersonality is being used to export illnesses internationally, as though they constituted universal entities, when in fact such illnesses are partly the product of Anglo-American social and cultural conventions.

SUMMARY AND CONCLUSIONS

In the field of ethnomedicine, problems of illness and medical care are studied in different societies with an emphasis on social and especially cultural factors. I use an ethnomedical look at Anglo-American psychiatry to draw attention to what I call its social "problematique." This is meant to emphasize the necessary link that psychiatry has with problems of deviance and marginality, which are also the concern of regulatory and control agencies of the complex industrialized state. An ethnomedical exposition of this "problematique" requires that attention be given to historical factors bound up with industrialization, the evolution of a market economy, the growth of the asylum, and, indeed, the evolution of the discipline of psychiatry as an institution for the control and regulation of mental illness. The continuing link that psychiatry has with socially problematic behaviors is mirrored in its special definition of illness, a definition that distinguishes psychiatry from other medical disciplines. The criteria of psychiatric illness remain anchored in the self and symbolic behavior despite the general consensus that many such illness behaviors have a genetic basis, are conditioned by brain processes, require a neuroscience for their understanding, and can be controlled if not rectified through the use of psychopharmacological agents. The social "problematique" of Anglo-American psychiatry is, in many respects, a necessary feature of its rationale, history, and practice. Contemporary developments involving the nosology and epidemiology of psychiatric illness reflect cultural biases inherent in the social "problematique" of Anglo-American psychiatry and should ideally be recognized. The existence of such a "problematique" and of its necessary link with cultural conventions is likely to retard and hinder if not preclude the achievement of a truly universal science of psychiatry.

REFERENCES

1. Young A: Some implications of medical beliefs and practices for social anthropology. *Am Anthropologist* 1976; 78:5-24
2. Kleinman A: Patients and Healers in the Context of Culture: An Exploration of the Borderland Between Anthropology, Medicine, and Psychiatry. Berkeley, University of California Press, 1980
3. Fabrega H Jr: Toward a theory of human disease. *J Nerv Ment Dis* 1976; 162:299-312
4. Hughes CC: Medical care, section I: ethnomedicine, in *International Encyclopedia of the Social Sciences*, vol 10. Edited by Sills DL. New York, Macmillan, 1968
5. Hallowell AI, Callender C: The self, society and culture in phylogenetic perspective, in *Evolution After Darwin*, vol II: The Evolution of Man. Edited by Tax S. Chicago, University of Chicago Press, 1960
6. Geertz C: *The Interpretation of Culture*. New York, Basic Books, 1973
7. Fabrega H Jr: *Disease and Social Behavior: An Interdisciplinary Perspective*. Cambridge, Mass, MIT Press, 1974
8. Lewis G: *Knowledge of Illness in a Sepik Society: A Study of the Gnau*, New Guinea. Atlantic Highlands, NJ, Humanities Press, 1975
9. Leslie C (ed): *Asian Medical Systems*. Berkeley, University of California Press, 1976
10. Press I: Problems in the definition and classification of medical systems. *Soc Sci Med* 1980; 14B:45-57
11. Rubin S: *Medieval English Medicine*. Totowa, NJ, Barnes & Noble, 1974
12. Debus AG: *Medicine in Seventeenth Century England*. Berkeley, University of California Press, 1974
13. Webster C: *The Great Instauration: Science, Medicine and Reform, 1626-1660*. New York, Holmes & Meier, 1975
14. Webster C (ed): *Health, Medicine and Mortality in the Sixteenth Century*. New York, Cambridge University Press, 1979
15. Porter R (ed): *Patients and Practitioners*. Cambridge, Cambridge University Press, 1985
16. Conrad P, Schneider JW: *Deviance and Medicalization*. New York, Merrill, 1980
17. Fabrega H Jr: The position of psychiatric illness in biomedical theory: a cultural analysis. *J Med Philos* 1980; 5:145-168
18. Fabrega H Jr: The position of psychiatry in the understanding of human disease. *Arch Gen Psychiatry* 1975; 32:1500-1512
19. Berrios G: The psychopathology of affectivity: conceptual and historical aspects. *Psychol Med* 1985; 15:745-758
20. Berrios G: Descriptive psychopathology: conceptual and historical aspects. *Psychol Med* 1984; 14:303-313
21. Fabrega H Jr: Psychiatric diagnosis: a cultural perspective. *J Nerv Ment Dis* 1987; 175:383-394
22. Reiser SJ: *Medicine and the Reign of Technology*. Cambridge, Cambridge University Press, 1978
23. Mautitz RC: *Morbid Appearances: The Anatomy of Pathology in the Early Nineteenth Century*. New York, Cambridge University Press, 1987
24. Foucault M: *Madness and Civilization*. New York, Pantheon, 1965
25. Connelly M: *Managing the Mind: A Study of Medical Psychology in Early Nineteenth-Century Britain*. New York, Tavistock Publications, 1983
26. Grob G: *Mental Institutions in America: Social Policy to 1875*. New York, Free Press, 1973
27. Scull A: *Museums of Madness: The Social Organization of Insanity in Nineteenth Century England*. New York, St Martin's Press, 1979
28. Rothman D: *The Discovery of the Asylum*. Boston, Little, Brown, 1971
29. Clarke B: *Mental Disorder in Earlier Britain*. Aberystwyth, University of Wales Press, 1975
30. Walker N: *Crime and Insanity in England*, vol 1: The Historical Perspective. Edinburgh, Edinburgh University Press, 1968
31. Walker N, McCabe S: *Crime and Insanity in England*, vol 2: New Solutions and New Problems. Edinburgh, Edinburgh University Press, 1973
32. Donzelot J: *The Policing of Families*. New York, Pantheon, 1979
33. Ingleby D: Mental health and social order, in *Social Control and the State: Comparative and Historical Essays*. Edited by Cohen S, Scull AT. New York, St Martin's Press, 1983
34. Ingleby D: Understanding mental illness, in *Critical Psychiatry: The Politics of Mental Health*. Edited by Ingleby D. New York, Pantheon, 1980
35. Kovel J: The American mental health industry. *Ibid*
36. Baruch G, Treacher A: *Psychiatry Observed*. London, Routledge & Kegan Paul, 1978

37. Sedgwick P: *Psycho Politics*. London, Pluto Press, 1982
38. Hare E: Was insanity on the increase? the fifty-sixth Maudsley lecture. *Br J Psychiatry* 1983; 142:439-455
39. Scull A: Was insanity increasing? a response to Edward Hare. *Br J Psychiatry* 1984; 144:432-436
40. Fabrega H Jr: The self and schizophrenia. *Schizophr Bull* (in press)
41. Spitzer S, Scull AT: Social control in historical perspective: from private to public response to crime, in *Corrections and Punishment*. Edited by Greenberg DF. New York, Sage, 1977
42. Cohen S, Scull AT: Social control in history and sociology, in *Social Control and the State: Comparative and Historical Essays*. Edited by Cohen S, Scull AT. New York, St Martin's Press, 1983
43. Rothman D: Social control: the uses and abuses of the concept. *Ibid*
44. Scull A: Humanitarianism or control: some observations on the historiography of Anglo-American psychiatry. *Ibid*
45. Wootton B: *Social Science and Social Pathology*. New York, Macmillan, 1959
46. Kitztrie NN: *The Right to Be Different: Deviance and Enforced Therapy*. Baltimore, Johns Hopkins Press, 1972
47. Foucault M: *Discipline and Punishment: The Birth of the Prison*. Translated by Sheridan A. New York, Random House, 1979
48. Lasch C: *Haven in a Heartless World: The Family Besieged*. New York, Basic Books, 1977
49. Bynum WF: Rationales for therapy in British psychiatry, 1780-1835, in *Madhouses, Mad-Doctors and Madmen*. Edited by Scull AT. Philadelphia, University of Pennsylvania Press, 1981
50. Porter R: The rage of party: a glorious revolution in English psychiatry? *Med Hist* 1983; 27:35-50
51. Thomas K: *Religion and the Decline of Magic*. New York, Macmillan, 1975
52. MacDonald M: *Mystical Bedlam: Madness, Anxiety and Healing in Seventeenth-Century England*. Cambridge, Cambridge University Press, 1981
53. Sawyer RW: Patients, Healers, and Disease in the Southeast Midlands, 1597-1634: University Microfilms Number ADG86-21929. *Dissertation Abstracts International* 47(A):3545
54. Walker DP: *Unclean Spirits: Possession and Exorcism in France and England in the Late Sixteenth and Early Seventeenth Centuries*. Philadelphia, University of Pennsylvania Press, 1981
55. Gottfried RS: *Doctors and Medicine in Medieval England*. Princeton, NJ, Princeton University Press, 1986
56. Neugebauer R: Treatment of the mentally ill in medieval and early modern England: a reappraisal. *J Hist Behav Sci* 1978; 14: 158-169
57. Kroll J: A reappraisal of psychiatry in the middle ages. *Arch Gen Psychiatry* 1973; 29:276-283
58. Cipolla CM: *Public Health and the Medical Profession in Renaissance Italy*. New York, Cambridge University Press, 1976
59. Park K: *Doctors and Medicine in Early Renaissance Florence*. Princeton, NJ, Princeton University Press, 1985
60. Fabrega H Jr, Silver DB: *Illness and Shamanistic Curing in Zinacantan*. Stanford, Calif, Stanford University Press, 1973
61. Smith R: *Trial by Medicine*. Edinburgh, Edinburgh University Press, 1981
62. Kaye JM: The early history of murder and manslaughter. *Law Quarterly Rev* 1967; 83:365-395, 569-601
63. Platt AM, Diamond BL: The origins and development of the wild beast concept of mental illness and its relation to the theories of criminal responsibility. *J Hist Behav Sci* 1965; 1:355-367
64. Sayre FB: *Mens rea*. *Harvard Law Rev* 1931-1932; 45:974-1026
65. Langbein JH: *The criminal trial before the lawyers*. University of Chicago Law Rev 1978; 45:263-316
66. Moran R: The origin of insanity as a special verdict: the trial for treason of James Hadfield (1800). *Law and Society Rev* 1985; 19:487-519
67. Eigen JP: Historical developments in psychiatric forensic evidence: the British experience. *Int J Law Psychiatry* 1983; 6: 423-429
68. Foucault M: About the concept of the "dangerous individual" in 19th-century legal psychiatry. *Int J Law Psychiatry* 1978; 1: 1-18
69. Zola IK: Medicine as an institution of social control. *Sociol Rev* 1972; 20:487-504
70. Strong PM: Sociological imperialism and the profession of medicine. *Soc Sci Med* 1979; 13A:119-215
71. Zola IK: In the name of health and illness: on some sociopolitical consequences of medical influence. *Soc Sci Med* 1975; 9: 83-87
72. Hoebel EA: *The Law of Primitive Man*. New York, Atheneum Press, 1983
73. Fabrega H Jr: The function of medical systems. *Perspect Biol Med* 1976; 20:108-119
74. Fabrega H Jr: The need for an ethnomedical science. *Science* 1975; 189:969-975
75. Fabrega H Jr: The biological significance of taxonomies of disease. *J Theor Biol* 1976; 63:191-216
76. Fabrega H Jr: The scope of ethnomedical science. *Cult Med Psychiatry* 1977; 1:201-228
77. Fabrega H Jr: Ethnomedicine and medical science. *Med Anthropology*, spring 1978, pp 11-28
78. Fabrega H Jr: The idea of medicalization: an anthropological perspective. *Perspect Biol Med* 1980; 24:129-142
79. Fabrega H Jr: Culture, biology and the study of disease, in *Biocultural Medicine*. Edited by Rothschild H. New York, Academic Press, 1981
80. Showalter E: *The Female Malady: Women, Madness and English Culture, 1830-1980*. New York, Pantheon Books, 1985
81. Johnson TM: Premenstrual syndrome as a Western culture-specific disorder. *Cult Med Psychiatry* 1987; 11:337-356
82. Swartz L: Anorexia nervosa as a culture-bound syndrome. *Soc Sci Med* 1985; 20:725-730
83. Ritenbaugh C: Obesity as a culture-bound syndrome. *Cult Med Psychiatry* 1982; 6:347-361
84. Littlewood R, Lipsedge M: The butterfly and the serpent: culture, psychopathology and biomedicine. *Cult Med Psychiatry* 1987; 11:289-335
85. Kleinman A: *Social Origins of Distress and Disease: Depression, Neurasthenia, and Pain in Modern China*. New Haven, Yale University Press, 1986
86. Bloch S: The Political Misuse of Psychiatry in the Soviet Union, in *Psychiatric Ethics*. Edited by Bloch S, Chodoff P. New York, Oxford University Press, 1981
87. Kaplan M: A woman's view of DSM-III. *Am Psychol* 1983; 38: 786-792
88. Lambo TA: Schizophrenic and borderline states, in *Transcultural Psychiatry*. Edited by DeReuck AUS, Porter R. Boston, Little, Brown, 1965
89. Wig N: DSM-III: a perspective from the Third World, in *International Perspectives in DSM-III*. Edited by Spitzer RL, Williams JBW, Skodol AE. Washington, DC, American Psychiatric Press, 1983
90. Wig NN: Standardized assessment in developing countries. *Acta Psychiatr Belg* 1985; 85:429-433
91. Sartorius N, Jablensky A, Korten A, et al: Early manifestations and first contact incidence of schizophrenia in different cultures. *Psychol Med* 1986; 16:909-928
92. Fabrega H Jr: Problems implicit in the cultural and social study of depression. *Psychosom Med* 1974; 36:377-398
93. Kleinman A: Depression, somatization and the new cross-cultural psychiatry. *Soc Sci Med* 1977; 11:3-10
94. Fabrega H Jr: Culture and psychiatric illness: biomedical and ethnomedical aspects, in *Cultural Conceptions of Mental Health and Therapy*. Edited by Marsella AJ, White GM. Dordrecht, The Netherlands, D Reidel, 1982
95. Fabrega H Jr: Neurobiology, culture and behavior disturbances: an integrative review. *J Nerv Ment Dis* 1979; 167:467-474
96. Fabrega H Jr: Cultural relativism and psychiatric illness. *J Nerv Ment Dis* (in press)
97. Kleinman A, Good B (eds): *Culture and Depression: Studies in the Anthropology and Cross Cultural Psychiatry of Affect and Disorder*. Berkeley, University of California Press, 1985

Borderline Personality Disorder, Boundary Violations, and Patient-Therapist Sex: Medicolegal Pitfalls

Thomas G. Gutheil, M.D.

The author addresses the issue of sexual relations between therapist and patient and the related boundary violations that are involved in such relations. He points out that patients with borderline personality disorder are particularly likely to evoke boundary violations, including sexual acting out. These patients apparently constitute the majority of patients who falsely accuse therapists of sexual involvement. Therapists who are aware of patterns of errors in therapy and countertransference—through education, anticipation, and forewarning—can avert the serious outcomes that result from these errors.

(Am J Psychiatry 1989; 146:597–602)

When you touch the patient, therapy is over.

—Elvin Semrad, M.D. (personal communication)

In an earlier review based on forensic and consultative experience (1), I addressed certain medicolegal difficulties that emerged in clinical work with patients who have borderline personality disorder. The present review, also based on empirical findings, addresses an important area omitted from detailed consideration in the earlier study: sexual relations between therapist and patient and the related boundary violations commonly seen in conjunction with such relations. I have three points to make here: 1) Patients with borderline

personality disorder are particularly likely to evoke boundary violations of various kinds, including sexual acting out in the transference-countertransference. 2) Patients with borderline disorder apparently constitute the majority of those patients who falsely accuse therapists of sexual involvement. (False accusations represent a minuscule fraction of total allegations; the accusation is usually true.) 3) Therapists can benefit from awareness of certain repeating patterns of errors in therapy and countertransference responses. With this awareness, they can avert the serious outcomes that result from such errors, such as trauma to the patient and/or highly destructive litigation.

One caveat is necessary to prevent misunderstanding. To study the patient-therapist dyad in clinical terms is not the same as indicting the patient (blaming the victim) for some malfeasance, nor is it the same as explaining away, exonerating, or excusing the therapist's behavior. I believe that sex with a patient is never acceptable. This article aims to alert clinicians to a potential pitfall in order to prevent its occurrence.

THE LEGAL CONTEXT OF MALPRACTICE

In recent years, case law (*Roy v. Hartogs* [2], for example) has reflected agreement with the ethical codes of all mental health professional societies that sexual relations between clinicians and their patients are at least unethical and, under rare circumstances, criminal. Such relations represent a deviation from the standard of care and a basis for a finding of malpractice if the other requisite elements (damages, for example) are present (3). Case law dramatically fails, however, to reflect the actual scope of the problem (4–7) because of the large number of episodes never reported at all and the substantial number of filed legal cases—probably but not provably the majority—that are settled out of court. (An unknowable but probably small

Received Aug. 23, 1988; accepted Nov. 23, 1988. From the Program in Psychiatry and the Law, Massachusetts Mental Health Center. Address reprint requests to Dr. Gutheil, Massachusetts Mental Health Center, 74 Fenwood Rd., Boston, MA 02115.

The author thanks members of the Program in Psychiatry and the Law for helpful comments; members of the McLean Forensic Seminar; and Drs. Alan A. Stone, Paul S. Appelbaum, Axel Hoffer, and Douglas Ingram.

Copyright © 1989 American Psychiatric Association.

fraction of these cases might have been settled for legal strategic reasons even though the clinician was not culpable.)

For symmetry, note that Stone (8) has offered a typology of therapists and situations most commonly associated with patient-therapist sex, and others, such as Gartrell et al. (4), have empirically studied the therapists involved. In contrast, the present review examines the other side of the dyad and the pathological interaction between patient and therapist.

THE CLINICAL CONTEXT: RELEVANT BORDERLINE PSYCHODYNAMICS

The psychodynamics of borderline personality disorder have been well described elsewhere (by Kernberg [9] and Shapiro [10], for example) and will not be rehearsed here. For completeness, note that nondynamic issues may play a role in accounting for the high numbers of patients with borderline personality disorder who are involved in patient-therapist sex. It may be important (Alan A. Stone, M.D., personal communication) that psychotic patients are not perceived as attractive and that neurotic patients are clear enough to know better than to become sexually involved. Thus, the field may be left to patients with borderline personality disorder through a kind of diagnostic default, as it were.

In any event, dynamic factors are clearly powerfully operative in the cases described in the literature. Empirically, those features of patients with borderline personality disorder which are most relevant here are borderline rage, neediness and/or dependency, boundary confusion, and manipulateness and entitlement.

Borderline Rage

Borderline rage is an affect that appears to threaten or intimidate even experienced clinicians to the point that they feel or act as though they were literally coerced—moved through fear—by the patient's demands; they dare not deny the patient's wishes. Such pressure may deter therapists from setting limits and holding firm to boundaries for fear of the patient's volcanic response to being thwarted or confronted. Of course, such fear ultimately derives from the therapist's conflicts over sadistic countertransference feelings, which patients with borderline personality disorder are particularly prone to evoke.

At other times, therapists who would ordinarily reflect back personal inquiries about themselves may feel actually trapped or pressured by the patient's potential rage into unusual and inappropriate degrees of social interaction with the patient or of self-disclosure, such as discussing their own marital difficulties. Intimidation may be further reinforced by latent and implicit or overt suicide threats.

In a different context the patient with borderline personality disorder may express rage in a vengeful

manner by filing a specious suit. As will be explored later in this paper, this particular form of vengeful hostility predominates in the group of false accusations.

Neediness and/or Dependency

Neediness and/or dependency are dynamics that call forth the therapist's nurturant side, at times in ways that foster overinvolvement or overinvestment. The rescue fantasy—common if not universal in trainees—appears to me to occur particularly frequently in treating those patients with borderline personality disorder who manifest a helpless, waif-like demeanor (1). The clinician may experience pressure not to disappoint or abandon the patient "as everyone else has done."

In a related manner the patient may wishfully draw from therapy the experience of being promised something—being offered membership in the therapist's idealized family, for example. Smith (11) has perceptively noted that some patients cherish a related wish, which he termed the golden fantasy: the wishful belief that the therapist will gratify *all* needs, not just therapeutic ones. Needless to add, a reciprocal narcissistic fantasy may motivate the therapist: the wish to be everything to the patient.

In this regard, Judith Herman, M.D. (personal communication), pointed out that since so many patients with borderline personality disorder have histories of sexual abuse they may have been conditioned to interact with significant others on whom they depend in eroticized or seductive ways. This learned response might provide some of the driving force for boundary violations.

Boundary Confusion

Under stress, patients with borderline personality disorder may lose sight of the me-thee boundary and—through such recognized mechanisms as fusion and projective identification—may induce similar confusion in therapists. This confusion may derive from patients' own boundary-blurring interpersonal manner. If the therapist colludes in such boundary confusion, reciprocal perceptions of both the real therapist and the real patient may be powerfully influenced and distorted by the intense affects, longings, and wishes common in patients with borderline personality disorder.

It is just such vulnerability in this group of patients that calls for scrupulous—even overscrupulous—attention by the therapist to clarity of boundaries and to preservation of the professional nature of the relationship.

Manipulateness and Entitlement

Patients with borderline personality disorder who are dysfunctional in many areas of life may still preserve intact powerful interpersonal manipulative skills. They may still be capable of getting even experienced professionals to do what they should know better than to do or—all too commonly—what they do know bet-

ter than to do. Clinicians have rejected early sexual advances from patients with borderline personality disorder, pleading professionalism, only to succumb later, like the alcoholic who, flushed with success at passing a bar, goes back to toast the victory.

On this latter point, I have identified a repeating theme in clinical contexts such as teaching conferences, consultations, and private inquiries. The therapist's near-conscious awareness of deviating from the standards of care, the therapist's countertransference guilt, even the therapist's awareness of overt wrongdoing—all are commonly conveyed by the therapist remarking at the outset of a conference or consultation, "I ordinarily don't do this . . ." or "While I don't usually do this with my patients . . .," or even, "Although I really didn't think I should be doing this . . ." and similar introductory comments. I view these remarks as pathognomonic of a likely countertransference trouble spot with a probably borderline patient, since the latter appears to generate and invite "not my usual" behavior. This situation appears to draw some of its force from the narcissistic entitlement and consequent sense of specialness of the patient with borderline personality disorder, in which the therapist may wish to share (1, 12, 13). This specialness may tempt the therapist to make exceptions for both the patient and himself or herself, to the detriment of both parties. Some of the most destructive dyadic relationships may begin as a mutual admiration society, not recognized as an idealizing transference (14) and its countertransference complement. The doctor, already idealized, is further invited to share in the patient's specialness through a narcissistic seduction.

The narcissistic isolation of the dyad that results from this sort of misalliance appears to account in part for the failure of so many of these therapists to obtain consultation and even to use their own critical judgment. It is as though such measures would break the fragile magic bubble in which all this gratification is occurring.

SOME CLINICAL MATERIAL

To illustrate the points in this paper I will use actual but disguised cases that I reviewed in the context of either malpractice litigation (28 cases) or forensic consultations (dozens) to clinicians or patients. All of the cases I will use involved male therapists and female patients with borderline personality disorder (the most common pairing nationally). In the service of confidentiality, all legal cases discussed have either been resolved (won, lost, settled, etc.), dropped, or dismissed; more than 1 year with no further news or follow-up from the consultee has elapsed for all consultations described.

Some generalizations at the outset may be helpful. All of these cases, true and false accusations alike, were clinically mismanaged in important ways, most commonly through failure to attend to boundaries and to the patients' need for clarity. Thus, as is so often the case, an ostensibly legal issue rests on a clinical one. In

some cases the mismanagement appeared to represent the kind of lapse not uncommon even for experienced clinicians in treating these difficult patients; in others, lack of experience, frank ignorance of essential principles of treatment of patients with borderline personality disorder, or countertransference difficulties seemed to predominate.

An interesting element in a number of cases was the patient's history of previous physical and/or sexual abuse. Conceivably, some element of a repetition compulsion was operating there, but the evidence is not decisive on this point.

To bring some validity to the often complex issue of which allegations are true and which are false, I have identified as true those accusations which have been admitted and/or acknowledged by the therapist, and as false those cases in which either the patient retracted the claim and identified it as false or the patient admitted to a disinterested third party that the claim was specious. Although recognizing that this selection method still does not guarantee validity, I believe it will offer sufficient reliability to permit the heuristic implications to be drawn.

False Accusations: Rare Events

To begin for convenience with the far smaller group, false accusations appear to be the product of borderline rage, expressed as vengeful action, coupled with a disregard for truth that is apparently self-justified by the strength of the affect. Snyder (15) discussed this subject under the rubric of *pseudologia fantastica* or pathological lying, including material related to sexual fantasies. He suggested that this kind of lying may feed self-esteem, serve primitive denial or projective identification, or represent transient loss of reality testing. It is important to consider the context in which such an accusation occurs.

Case 1. A patient with borderline personality disorder became enraged at her physician because she felt he was treating her in a disrespectful manner: in her words, "like a welfare case." She later brought suit against him for sexual molestation. During the discovery phase of the lawsuit, an investigator, who was not known to the patient, visited her under false pretenses and obtained (probably illegally) a tape recording of her admitting that she had been furious with the physician and had fabricated this story in a scheme to "get him good."

Case 2. A psychiatrist had been excessively but not sexually involved with a patient with borderline personality disorder in ways that fed her magical wishes to be a part of his family. He rejected the patient's request to see him on a major holiday, pleading family commitments. Her fantasy rudely shattered, the enraged patient brought litigation for sexual abuse and other specious claims but confided in a fellow patient, who revealed the deceit to the attorney.

Other triggers for false accusations have included borderline rage at bill collection practices, at the ther-

apist's termination of therapy, and at being generally mistreated.

Boundary Violations

Patients with borderline personality disorder are known for their frequent difficulties with boundaries and limits, whether referring to their own ego boundaries, the realistic limitations of reality, another person's capacities, or interpersonal space (9). What may be less universally acknowledged is that patients with borderline personality disorder possess the ability, as it were, to seduce, provoke, or invite therapists into boundary violations of their own in the countertransference (16). Thus, the therapists' psychological defects and educational deficiencies aside, these boundary violations seem to derive at least in part from the dynamic forces addressed earlier in this paper. I repeat that these empirical observations neither blame the victim nor exonerate the therapist. They must, however, be understood as temptations to be avoided to prevent mishap.

Case 3. In addition to doing therapy, a psychiatrist gave a patient with borderline personality disorder hundreds of dollars; gave her medications from a supply he had prescribed to himself; and had her stay, at his invitation, in his own house—in a spare bedroom—during a housing "crisis." The psychiatrist slept on the floor in front of the spare bedroom door so that the patient could not leave without his knowing it. All of these actions were rationalized as being in response to the patient's needs.

Given that patients with borderline personality disorder might well require unusual degrees of clarity about the therapist's role and particular vigilance concerning possible distortions of his or her role functions, this boundary-blurring behavior by the therapist represents an obvious and serious deviation. Similar examples follow.

Case 4. A psychiatrist invited a hospitalized patient to stay rent free at a guest house on his property as a halfway step to discharge to outpatient status.

Case 5. A psychiatrist who was in the habit of having meetings with a patient with borderline personality disorder two to three times a week invited her to see him daily following the week he was away in "compensation." He remarked, "I let her come as frequently as she wanted because I did not want to disappoint her."

These two examples appeared to have as subtext the therapist's conflict over aggression in setting limits and fear of the patient's consequent rage. Similar dynamics appear to foster exchanging of gifts, real and symbolic, between patient and therapist.

Case 6. A psychiatrist participated in long late-night telephone calls to and from a patient with borderline personality disorder while his wife and children slept. He remained blind to the erotic potential of this habit. He also shared many

personal, marital, and financial troubles of his own with the patient.

Case 7. A psychiatrist asked an editorially gifted patient to work with him on improving his professional articles for publication.

Patient-Therapist Sex

Clearly, sex between patient and therapist represents, among other things, a severe boundary violation. Its drama, its often traumatic effects on the patient and on future therapy (17–19), and a number of ambiguities in the medicolegal area set this behavior somehow apart.

A surprisingly and regrettably large number of psychiatrists appear to believe, quite incorrectly, that sex with a patient is acceptable as long as therapy has been terminated first. (Some believe it is acceptable if therapy has been terminated with referral.) This is clearly false. The therapist who stops treatment on June 30 and has sex with the patient on July 1 is clearly violating the fiduciary relationship just as egregiously as if the sex had occurred on June 29.

Audiences at risk management seminars occasionally ask, "How long after therapy is over may one date a patient?" The only unassailable answer, in my opinion, is Never. This restraint represents the only infallible approach to liability prevention in this unclear area.

Regrettably, desirable clarity about sexual behavior may be lost by even experienced clinicians, as in the next example.

Case 8. A patient with very primitive borderline personality disorder was being treated on an inpatient unit. Unit staff had evolved a plan involving giving the patient hugs—a regressive response—as a reward, paradoxically, for mature and realistic behavior, despite the fact that this patient had a known history of major psychotic regressions, confusions of fact and fantasy and of intimacy and sexuality, sexual abuse by her family in childhood, and, on one occasion, confessing that she had fabricated sexual accusations for attention. Despite this background, her experienced therapist acknowledged giving her, on various occasions, a large number and variety of hugs, including social hugs, reassurance hugs, goodbye hugs, and congratulatory hugs. On one previous occasion in reaction to a threatened termination of therapy this patient had explicitly accused this therapist of sexual advances. When confronted she retracted the accusation as false and attributed it to a wish to punish yet keep the therapist.

On the particular occasion in question the patient had threatened to commit suicide in the context of a planned termination of therapy and was being seen for a second, extra appointment on the same day as her regular one. During this very session the patient showed impulsivity, loose associations, and serious regression. At the end of the session, the patient requested a goodbye hug and the therapist acquiesced and attempted a social hug. The patient suddenly began to breathe heavily and thrust her pelvis, then drew a vibrator from her purse, which led the therapist to disengage and set a limit. The patient regressed, sobbing and threaten-

ing suicide, but refused hospitalization. She then attempted to persuade the therapist to take her home himself rather than have her face the "unsavory characters" found at the bus station. He delayed several times, but then he drove her home from this tumultuous, out-of-control session.

The therapist later stated that he remained unclear about whether all this activity related to termination of therapy or not. His report of the incident reads, "*Contrary to [my] usual policy of making a termination session final (especially with a borderline patient) because of the possibility of a misunderstanding, [I] told her [I] would call her to check if she was okay and, if she wanted it, . . . set up one more appointment*" (my italics). The patient subsequently accused this doctor of sexual relations both in his office and in the car on the ride home.

Although the patient later retracted as false the specific accusations, I would suggest that the hugging alone, from her viewpoint, represented sexual behavior with this patient. It was a clear boundary violation in this context. The patient's history practically guaranteed confusion as to what was and what was not sex, and the therapist's behavior was ambiguous in the very area where the patient already had problems with clarity. The record, moreover, strongly suggests that the patient was directing the sessions to whatever issues she thought would get the doctor to hug her. As therapy for other goals, the sessions may well have been meaningless. Expecting this patient to distinguish among hugs, no matter how therapeutically rationalized, appears quite unrealistic.

Given the fact that this therapist had already been explicitly accused of sexual misconduct by this very patient, his later boundary violations appear incomprehensible, as well as ill-advised, no matter how non-constructively gratifying for both parties this activity may have been. I infer from the data that the patient's desperation, suicide threats, sense of urgency, and neediness were sufficient to overcome even heightened caution.

Case 9. A psychiatrist, responding to the alleged sexual naivete of a patient with borderline personality disorder, gave her anatomy lessons on both their naked bodies. He reasoned that as long as they stopped short of intercourse, the behavior was not really sex and thus acceptable. Over time, predictably, the relationship eventually came to include intercourse.

Case 10. Rationalizing the press of scheduling, a psychiatrist saw a patient with borderline personality disorder in the hospital daily for 2- and 4-hour appointments, sometimes running from 2:00 to 6:00 a.m. The relationship eventually became sexual.

RECOMMENDATIONS

"I don't understand why every psychiatrist is not fully forewarned about both sex and rage" (Cornelia B. Wilbur, personal communication).

A number of factors combine to foster the kinds of

blind spots and unfortunate consequences outlined in this paper in regard to patients with borderline personality disorder. One such factor, in keeping with Dr. Wilbur's rueful lament, is the relative decline in teaching about psychodynamics, transference-countertransference, and similar issues in many training programs today. For example, the inpatient unit involved in case 8 provided a number of different therapies and therapeutic ideologies but no dynamic ones.

Clearly, such understanding, although useful and necessary in averting problems, is not sufficient to explain or avert these problems. Psychoanalysts, after all, are not immune to sexual involvement with their patients. Dynamic instructional approaches are, moreover, of no avail with consciously exploitative, predatory therapists, of the sort that Stone (8) described. Fortunately, those individuals are comparatively rare, but weeding them out from the profession would be a laudable goal. Even some faint awareness of transference, with its power to produce flattering attitudes in the patient, and of countertransference, with its potential to trigger the feeling that the therapist and only the therapist can save the patient (drive home, feed, love, provide with the "right kind of sex"), might offer young therapists needed perspective, both at the crisis point and at later junctures in their work.

Some such minimal educational efforts, no matter how antianalytic the training program, appear to be a necessary survival-oriented part of the modern curriculum. In particular, trainees should be told and shown that the impulse to make an exception—especially with patients with borderline personality disorder—no matter how plausibly rationalized, is suspect and should set off red flags of caution. Didactic sessions on borderline personality disorder should include as warnings case examples such as those given here. Rescue fantasies should be described in nonjudgmental terms, and their operation and mastery should be explored.

Explicit instruction in practical management of treatment impasses such as those noted here (suicide threats, wishes to be driven someplace, etc.) is equally essential. I have referred to this management dimension as clinical administration (20). This involves alliance-based interaction and intervention in the patient's physical behavior, such as setting limits and placing some responsibility for the solution of reality problems on the patient.

From a preventive viewpoint, the clinician encountering a transference that becomes eroticized would do well to begin regularly presenting the case to a colleague, supervisor, or appropriate consultant. In addition to providing valuable input and perspective, such consultation opens the case up and avoids the dangerous insularity of the treatment dyad that often promotes boundary violations. Not only does this approach prevent the illusion that the dyad is encased in a magic bubble from forming but—through this very openness—may also offer some possible defense against false accusations of sexual misconduct.

Finally, reality issues such as the trauma to the patient (17) and the serious legal consequences should be articulated. Sex with a patient is ultimately bad for the patient, no matter how good it feels, and a malpractice suit for sex is devastating to the doctor's career, affecting registration and licensing. These deterrents should be explicitly described.

The educational approaches outlined here may be helpful for those situations where therapists are on the verge of losing perspective, succumbing to the force of countertransference, or simply getting carried away. Under those circumstances, education, anticipation, and forewarning may serve the clinician and the patient well.

REFERENCES

1. Gutheil TG: Medicolegal pitfalls in the treatment of borderline patients. *Am J Psychiatry* 1985; 142:9-14
2. *Roy v Hartogs*, 366 NYS 2d 297 (Civ Ct, NY, 1975); affirmed on condition of remittitur, 381 NYS 2d 587 (Sup Ct, NY, 1976)
3. Gutheil TG, Appelbaum PS: *Clinical Handbook of Psychiatry and the Law*. New York, McGraw-Hill, 1982
4. Gartrell N, Herman J, Olarte J, et al: Psychiatrist-patient sexual contact: results of a national survey, I: prevalence. *Am J Psychiatry* 1986; 143:1126-1131
5. Perry JA: Physicians' erotic and nonerotic physical involvement with patients. *Am J Psychiatry* 1976; 133:838-840
6. Kardener SH, Fuller M, Mensh IN: Characteristics of "erotic" practitioners. *Am J Psychiatry* 1976; 133:1324-1325
7. Kardener SH: Sex and the physician-patient relationship. *Am J Psychiatry* 1974; 131:1134-1136
8. Stone AA: *Law, Psychiatry, and Morality: Essays and Analysis*. Washington, DC, American Psychiatric Press, 1984
9. Kernberg O: *Borderline Conditions and Pathological Narcissism*. New York, Jason Aronson, 1975
10. Shapiro ER: The psychodynamics and developmental psychology of the borderline patient: a review of the literature. *Am J Psychiatry* 1978; 135:1305-1315
11. Smith S: The golden fantasy: a regressive reaction to separation anxiety. *Int J Psychoanal* 1977; 58:311-324
12. Pollack I, Battle W: Studies of the special patient. *Arch Gen Psychiatry* 1963; 9:344-350
13. Main TF: The ailment. *Br J Med Psychol* 1957; 30:129-145
14. Adler G: Valuing and devaluing in the psychotherapeutic process. *Arch Gen Psychiatry* 1970; 22:454-461
15. Snyder S: Pseudologia fantastica in the borderline patient. *Am J Psychiatry* 1986; 143:1287-1289
16. Stone MH: Boundary violations between therapist and patient. *Psychiatr Annals* 1976; 6:670-677
17. Collins DT, Mebed AAK, Mortimer RL: Patient-therapist sex: consequences for subsequent treatment. *McLean Hosp J* 1978; 3:24-36
18. Ulanov AB: Follow-up treatment in cases of patient/therapist sex. *J Am Acad Psychoanal* 1979; 7:101-110
19. Apfel RJ, Simon B: Patient-therapist sexual contact: psychodynamic perspectives on the causes and results. *Psychother Psychosom* 1985; 43:57-62
20. Gutheil TG: On the therapy in clinical administration, part II: the administrative contract, alliance, ultimatum and goal. *Psychiatr Q* 1982; 54:18-25

Psychotherapy of Schizophrenia: An Empirical Investigation of the Relationship of Process to Outcome

Leonard L. Glass, M.D., Howard M. Katz, M.D.,
Robert D. Schnitzer, Ph.D., Peter H. Knapp, M.D.,
Arlene F. Frank, Ph.D., and John G. Gunderson, M.D.

The Boston Psychotherapy Study found no major differences in the effects of insight-oriented and supportive psychotherapies in the treatment of schizophrenia. The authors of the current study looked beyond the assignments to those treatment designations and used blindly rated transcripts of tape-recorded sessions to examine the relationship of therapist interventions and patient outcomes at 2 years. They found significant relationships between skillfully conducted psychodynamic exploration and greater improvements in negative symptom areas of schizophrenia. The authors note the limitations and implications of these findings for clinical practice and research.

(Am J Psychiatry 1989; 146:603-608)

Although the two different types of psychotherapy in the Boston Psychotherapy Study (1, 2) fostered similar overall outcomes, there were sufficient differences in the findings to lend support to the concept of specific differential effects. One type of therapy, reality-adaptive-supportive, had preferential effects on recidivism and role performance, whereas a contrasting form of treatment, expressive-insight-oriented, exerted modestly preferential effects in areas of ego functioning and cognition. This support for specific differential impacts emerged despite the fact that the expected differences between the two types of therapy in the amount of supportive techniques were not found, even though expressive-insight-oriented therapists differed from reality-adaptive-supportive therapists by meeting more frequently with their patients and by focusing more on unconscious motivations and undercurrents of feelings (1). This finding prompted us to undertake analyses that go beyond nominal assignment to expressive-insight-oriented or reality-adaptive-supportive therapies, i.e., analyses that explore whether spe-

cific types of therapeutic interventions are associated with specific types of outcomes.

In this paper we will report on the relationship between therapists' activities and patients' outcomes for those patients for whom we have more detailed psychotherapy process data. Using therapists' interventions that were blindly rated from transcripts of tape-recorded sessions, we explored the relationship of specific process factors to the 2-year outcomes among this group of patients with nonchronic schizophrenia.

METHOD

Methods used to select patients and therapists for the overall study are more fully described elsewhere (1). The therapists were all experienced in working with schizophrenic patients (averaging 10 years in practice), and the majority had had personal psychoanalyses. The subjects were all newly hospitalized, actively psychotic, but nonchronically ill patients who were given both clinicians' diagnoses and research diagnoses (3) of schizophrenia. Despite changing diagnostic standards, checks were made to assure that the sample would be within even narrow diagnostic criteria (1).

Therapists and patients were asked to audiotape all sessions to avoid the influence on performance during individual sessions of having only those selected sessions taped. Two consecutive sessions occurring 6 months after the start of treatment were transcribed in their entirety and served as the basis for rating therapist activity. These data were available for 39 subjects.

Twenty-two process rating scales focusing on therapist techniques and skills were used. These scales were selected after review of the rating schemes reported in the literature and relied heavily on those developed in the Pennsylvania Psychotherapy Study (4, 5). Scales were chosen to represent dimensions examined in previous research on dynamic psychotherapy with schizophrenic patients (6). All scales were given specific descriptive anchors for each of five scale points.

Seven experienced clinicians made process ratings from the transcripts. Each of these clinicians had at

Received July 15, 1987; revision received Sept. 22, 1988; accepted Nov. 3, 1988. From the Psychosocial Research Program, McLean Hospital. Address reprint requests to Dr. Glass, McLean Hospital, 115 Mill St., Belmont, MA 02178-9106.

Supported in part by NIMH grant MH-25246.

Copyright © 1989 American Psychiatric Association.

TABLE 1. Factor Analysis of Ratings of Two Psychotherapy Sessions Each for 39 Schizophrenic Patients

Factor	Loading of Variable	Percent of Variance Accounted for
Skillful dynamic exploration		41.3
Overall dynamic skill	0.90	
Sensitivity to undercurrents	0.88	
Responsiveness and/or adequacy of technique	0.85	
Empathy	0.68	
Focus on improving ego functions	0.65	
Softens conscience	0.64	
Emphasizes unconscious	0.63	
Focus on past	0.44	
Supportive activity		25.3
Self-expression	0.79	
Gives encouragement and/or reassurance	0.73	
Self-disclosure	0.62	
Is warm and giving	0.44	
Directive activity		13.4
Gives suggestions and/or advice	0.82	
Supports reality orientation	0.76	
Assertiveness	0.50	

least 60 hours of reliability training. Despite such training, the intraclass reliabilities calculated for all raters on 15 pairs of sessions were often weak (range=0.12–0.70, mean $r=0.46$, median $r=0.47$). As a result, the process ratings that were used in all analyses were derived from the ratings of at least two clinicians who made independent ratings on each tape and then met to reach consensus.

The interrelations of the 22 process variables were first examined by applying the principal components factor analysis of the Statistical Package for the Social Sciences (SPSS) (7) with an orthogonal (varimax) rotation to the ratings of the 39 sets of tapes. After all factors with an eigenvalue of less than 1.0 were deleted, three principal factors emerged: skillful dynamic exploration, supportive activity, and directive activity (table 1).

Skillful dynamic exploration had three major components: overall dynamic skill, sensitivity to undercurrents, and responsiveness and/or adequacy of the therapist's technique. Sensitivity to undercurrents was a measure of the therapist's attunement to the unexpressed preconscious and unconscious motivational background from which the patient's mood, thinking, and behaviors emerged. Responsiveness and/or adequacy of the therapist's technique was the rater's estimate of the relevance, consistency, and timing of the therapist's interventions. As shown in table 1, lesser contributions to the skillful dynamic exploration factor came from five other variables.

Supportive activity had four components. Self-expression measured the extent to which a therapist expressed emotional responses to the patient. Self-disclosure reflected whether therapists shared aspects of

their private lives and personal experiences. The therapist's providing encouragement and/or reassurance and being warm and giving were the other two components contributing to this factor.

Directive activity had three components, the leading element of which was the therapist's giving suggestions and/or advice. Support of a reality orientation reflected the emphasis therapists placed on their patients' adaptation to the environment and their encouragement of more realistic functioning. The third component, assertiveness, indicated that therapists presented their views in a forceful and straightforward manner. Therapists with higher directive activity ratings more clearly and explicitly attempted to shape their patients' behavior by actively advising, by reinforcing behaviors perceived as adaptive, and by an energetic, leading style.

The relationship between process and outcome was studied for 23 of the 39 patients. These 23 patients remained in treatment for at least 6 months, and their data included both tape recordings at 6 months and outcome at 2 years. The majority ($N=19$) had been given expressive-insight-oriented therapy; four had been given reality-adaptive-supportive therapy. We included these four patients to increase our small sample, to broaden the spectrum of therapist activities, and to increase the relevance of our findings to clinical practice. The 23 patients were similar in baseline psychopathology to the 20 patients for whom 6-month tape data were received but who did not remain in therapy for 2 years and to the four patients who remained in therapy for 2 years but for whom sufficient tapes were not available.

Outcome measures consisted of scores at 2 years on nine clusters of variables. The clusters were cognitive disorganization (Chronbach's $\alpha=0.61$, intraclass $r=0.95$), primary process thinking ($\alpha=0.90$, $r=0.81$), denial of illness ($\alpha=0.72$, $r=0.97$), ego weakness ($\alpha=0.53$, $r=0.94$), positive attitude ($\alpha=0.72$, r not applicable; self-report), global psychopathology ($\alpha=0.62$, $r=0.93$), anxiety-depression ($\alpha=0.85$, $r=0.91$), retardation-apathy ($\alpha=0.82$, $r=0.56$), and social dysfunction ($\alpha=0.75$, $r=0.88$). Appendix 1 shows their components. References, annotated descriptions, and reliabilities for the instruments listed in appendix 1 are given in Stanton et al. (1). Each domain included a number of discrete variables selected from the instruments administered blindly at baseline and at 24 months. The method for selecting and testing the psychometric adequacy of the outcome clusters is more fully described elsewhere (1). The nine outcome domains were chosen from the 15 used in the larger study to cover a range of nonoverlapping domains that reflect aspects of function considered to be targets of psychotherapy.

To examine the relationship between process and outcome, we first computed simple (zero-order) correlations between the three process measures and the nine outcome measures (table 2). We also computed the correlations between scores on each outcome mea-

TABLE 2. Simple Correlations^a of Psychotherapy Process With Outcome for 23 Schizophrenic Patients

Two-Year Outcome Variable	Correlation With Baseline Functioning	Correlation With Process Factor		
		Dynamic Exploration	Supportive Activity	Directive Activity
Cognitive disorganization	0.29	-0.04	-0.17	-0.16
Primary process thinking	0.15	-0.29	-0.16	0.26
Denial of illness	0.43 ^b	-0.58 ^c	0.08	0.11
Ego weakness	0.27	0.20	0.02	0.16
Positive attitude	0.12	0.20	0.02	0.20
Global psychopathology	0.18	-0.40 ^d	-0.14	-0.12
Anxiety-depression	0.67 ^e	0.47 ^b	-0.38 ^d	-0.33
Retardation-apathy	0.29	-0.49 ^b	0.07	-0.14
Social dysfunction	0.34	-0.29	0.01	-0.04

^aTwo-tailed; df range=16-20.^bp<0.05.^cp<0.01.^dp<0.10.^ep<0.001.

TABLE 3. Stepwise Regression Analysis of Process and Outcome of Psychotherapy for 23 Schizophrenic Patients

Item	Correlation Between Outcome Variable and Predictor Variables				Increment in Variance Accounted for by Predictor Variable
	R ²	R	F (df=2, 19) ^a	p	
Predictor variables for 2-year outcome of denial of illness	0.42	0.64	6.74	<0.01	
Baseline denial of illness					0.19 ^b
Dynamic explorative therapy					0.23 ^b
Predictor variables for 2-year outcome of global psychopathology	0.23	0.48	2.76	<0.10	
Baseline global psychopathology					0.03
Dynamic explorative therapy					0.20 ^b
Predictor variables for 2-year outcome of anxiety-depression	0.53	0.73	10.84	<0.001	
Baseline anxiety-depression					0.45 ^c
Directive therapy					0.09 ^d
Predictor variables for 2-year outcome of retardation-apathy	0.34	0.58	4.85	<0.05	
Baseline retardation-apathy					0.09 ^d
Dynamic explorative therapy					0.25 ^e

^adf=2, 18 for analysis of 2-year outcome of global psychopathology and baseline global psychopathology.^bp<0.05.^cp<0.001.^dp<0.10.^ep<0.005.

sure at baseline with scores on that measure at 2 years to get some idea of the stability of functioning over time. Next, we performed a series of stepwise multiple regression analyses to determine whether our three process measures of therapist activities could add to prediction of outcome after differences among patients in baseline levels of functioning on the respective variables were statistically eliminated. The multiple regression analysis thereby became our most telling analysis about the relationship of therapist activities to outcome in this sample. In these analyses we specified that baseline scores in each of the nine outcome domains be entered first because of their temporal primacy. Then the three process measures were entered in order of their predictive power, provided that they made at least a marginally significant contribution to the multiple regression analysis. This analysis allowed

us to see the relationship to outcome when all of the process measures were taken into account. The results of these analyses are presented in table 3.

RESULTS

The most striking findings from the simple correlation analysis (table 2) was the significant relationship between skillful dynamic exploration and better outcome. Specifically, higher levels of skillful dynamic exploration, assessed at 6 months, were associated with significantly lower levels of patient denial of illness and retardation-apathy and higher levels of anxiety-depression. Higher levels of skillful dynamic exploration were also associated with marginally lower levels of global psychopathology at 2 years. The only other no-

TABLE 4. Summary of Correlations Between Psychotherapy Process and Outcome Variables for 23 Schizophrenic Patients

Process Factor	Outcome Variables	Significance (p)	
		Simple (zero-order) Correlation	Increment in Outcome Variance Accounted for ^a
Dynamic explorative therapy	Reduced denial of illness	0.01	0.01
	Reduced global psychopathology	0.10	0.01
	Reduced retardation-apathy	0.01	0.005
	Increased anxiety-depression	0.01	n.s.
Supportive therapy	Reduced anxiety-depression	0.10	n.s.
Directive therapy	Reduced anxiety-depression	n.s.	0.10

^aBeyond that accounted for by baseline level of functioning.

table correlation was a trend between therapist supportive activity and lower levels of anxiety-depression.

The stepwise multiple regression analysis (table 3) confirmed the importance of skillful dynamic exploration in predicting outcome in the domains of denial of illness, global psychopathology, and retardation-apathy; for each area the predictive power of skillful dynamic exploration exceeded the predictive power of baseline measures. The association between skillful dynamic exploration and greater anxiety-depression was not found when baseline variations in anxiety-depression were controlled. However, a trend emerged for directive activity to be associated with greater reductions in anxiety-depression. Table 4 presents a summary of the correlations between process and outcome.

DISCUSSION

The difficulty in obtaining the data used in this report makes replication unlikely but underscores the value of learning whatever is possible from it. Nonetheless, limitations in the methodology point to the need for caution in interpreting the results. A major problem is the relatively small sample size, which limits generalizability and impinged on our statistical management. Specifically, our factor analysis might have come out differently with a different and larger sample, and it was not feasible to control for all baseline variables in doing the stepwise multiple regression analysis.

In addition to the problems associated with the sample size, other limitations in this study resulted from the relatively weak reliability of our process variables—a reflection of the era in which the study was done and the levels of inference required to assess clinically relevant therapeutic processes (8). A final problem in methodology is that questions could be raised about the representativeness of two consecutive sessions from 6 months and outcome measures at 2 years. These limitations notwithstanding, the results create, at a minimum, informed hypotheses derived from much better data than have previously been used to explore these issues for schizophrenic patients. The use of blind ratings of actual (as opposed to expected or

reported) therapist activities is a major advance over previous reports on psychotherapy of schizophrenia.

The finding that was most robust, most pertinent to the main study questions, and most clinically relevant is the relationship of skillful dynamic exploration to the 2-year outcome of these schizophrenic patients. Our skillful dynamic exploration factor primarily reflected the extent to which the therapist was judged to show a sound psychodynamic understanding and accurate attunement to patients' underlying concerns. A notable relationship emerged between skillful dynamic exploration and relatively large reductions in patient denial of illness, retardation-apathy, and global psychopathology assessed at 2 years. Indeed, the level of skillful dynamic exploration was an even better predictor of outcome in these domains than were pretreatment levels of disturbance in these same areas. The statistical significance of this relationship is particularly impressive in view of the constraints imposed by the small number of patients, length of observation, and the fact that most of the therapists were oriented toward dynamic exploration. The relationship between dynamic exploratory activity and reductions in the so-called negative symptoms of schizophrenia (9), such as retardation-apathy and denial of illness, is especially noteworthy insofar as these symptoms are generally unresponsive to psychopharmacological and other interventions and may be core aspects of schizophrenic psychopathology (10). These findings lend credence to the claims by psychodynamically oriented therapists that their activities should have a role in treating schizophrenic patients (11, 12).

The connection of skillful dynamic exploration with outcome is largely congruent with the earlier studies of Truax et al. (13–16). The therapist empathy and/or sensitivity component of our skillful dynamic exploration factor probably overlaps with the triad of empathy-genuineness-nonpossessive warmth that Truax et al. found to be associated with positive outcome in psychotherapy with schizophrenic patients. Certainly our results underscore the importance of empathic interactions that have been highlighted in recent years for psychoanalytic therapies by Kohut (17, 18). However, some of what Truax et al. identified as nonpossessive warmth corresponds more closely to our factor

of support, which in this study did not correlate with better outcome.

The findings of our factor analysis demonstrate the prominence of supportive and directive techniques in the work of these dynamically oriented therapists. The finding that high mean scores were given to primarily dynamic therapists for directive activity and supportive activity (data not presented) is consistent with that of others (19–21). Wallerstein (20) particularly emphasized the strong (and unexpected) contribution of supportive factors in psychoanalytic therapies of patients with serious ego weakness. Such results suggest that the distinction historically made between supportive and dynamic psychotherapy obscures the role played by supportive elements within psychoanalytic psychotherapies.

In line with this, the trend for directiveness to be associated with a greater reduction in anxiety-depression at 2-year follow-up makes clinical sense. One might expect that therapists who elect to direct patients rather than explore their difficulties will have different effects. By providing more active guidance in the real world, directive therapist activities could engender a less depressed and less apprehensive outlook in these patients. On the other hand, we have seen that greater dynamic exploratory activity was associated with larger improvements in the target symptoms that are more specific for schizophrenia (global psychopathology, denial of illness, and retardation-apathy). The different therapeutic emphases seem to address different aspects of patients' psychopathology and are associated with different types of outcome. As such, the results of the present analyses add support to the suggestion of differentiated types of impact of dynamic exploratory and supportive therapies that were noted in the main effect study (2).

This study provides empirical support for a specific relationship between a type of therapeutic process—skillful dynamic exploration—and specific aspects of outcome—denial of illness and withdrawal. The impression of an overall lack of main effect differences between the two types of therapy in our earlier report (2) appears to have concealed discrete processes within the therapies that have important and specific effects. This underscores the importance of more microscopic process versus outcome analyses for other comparative outcome studies, such as the National Institute of Mental Health Treatment of Depression Collaborative Research Program (22), where analyses of main effects have been disappointing.

REFERENCES

1. Stanton AH, Gunderson JG, Knapp PH, et al: Effects of psychotherapy in schizophrenia, I: design and implementation of a controlled study. *Schizophr Bull* 1984; 10:520–563
2. Gunderson JG, Frank AF, Katz HM, et al: Effects of psychotherapy in schizophrenia, II: comparative outcome of two forms of treatment. *Schizophr Bull* 1984; 10:564–598
3. Carpenter WT Jr, Strauss JS, Bartko JJ: Flexible system for the diagnosis of schizophrenia: report from the WHO International

- Pilot Study of Schizophrenia. *Science* 1973; 182:1275–1278
4. Mintz J, Luborsky L, Auerbach AH: Dimensions of psychotherapy: a factor analytic study of psychotherapy sessions. *J Consult Clin Psychol* 1971; 36:106–120
5. Luborsky L, Chandler M, Auerbach AH, et al: Factors influencing the outcome of psychotherapy: a review of quantitative research. *Psychol Bull* 1971; 75:145–185
6. Katz HM, Frank A, Gunderson JG, et al: Psychotherapy of schizophrenia: what happens to treatment dropouts. *J Nerv Ment Dis* 1984; 172:326–331
7. Nie NH, Hull CH, Jenkins JG, et al: *Statistical Package for the Social Sciences (SPSS)*, 2nd ed. New York, McGraw-Hill, 1975
8. Koenigsberg HW, Kernberg OF, Haas G, et al: Development of a scale for measuring techniques in the psychotherapy of borderline patients. *J Nerv Ment Dis* 1985; 173:424–431
9. Andreasen NC: Positive vs negative schizophrenia: a critical evaluation. *Schizophr Bull* 1985; 11:380–390
10. Carpenter WT, Heinrichs DW, Wagman AMI: Deficit and non-deficit forms of schizophrenia: the concept. *Am J Psychiatry* 1988; 145:578–583
11. Gomes-Schwartz B: Effective ingredients in psychotherapy: prediction of outcome from process variables. *J Consult Clin Psychol* 1978; 46:1023–1035
12. Gunderson JG: Controversies about the psychotherapy of schizophrenia. *Am J Psychiatry* 1973; 130:677–681
13. Truax C, Carkhuff R: *Toward Effective Counseling and Psychotherapy: Teaching and Practice*. Chicago, Aldine, 1967
14. Rogers CR, Gendlin GT, Kiesler DJ, et al: *The Therapeutic Relationship and Its Impact: A Study of Psychotherapy With Schizophrenics*. Madison, University of Wisconsin Press, 1967
15. Truax CB: Effects of client-centered psychotherapy with schizophrenic patients: nine-year pretherapy and nine-year posttherapy hospitalization. *J Consult Clin Psychol* 1970; 35:417–422
16. Truax CB, Mitchell KM: Research on certain therapist interpersonal skills in relation to process and outcome, in *Handbook of Psychotherapy and Behavior Change: An Empirical Analysis*. Edited by Garfield SL, Bergin AE. New York, John Wiley & Sons, 1971
17. Kohut H: *The Analysis of the Self*. New York, International Universities Press, 1971
18. Kohut H: *The Restoration of the Self*. New York, International Universities Press, 1977
19. Luborsky L, Singer B, Luborsky L: Comparative studies of psychotherapies: is it true that "everybody has won and all must have prizes"? *Arch Gen Psychiatry* 1975; 32:995–1008
20. Wallerstein R: *Forty-Two Lives in Treatment*. New York, Guilford Press, 1986
21. Waldinger RJ, Gunderson JG: *Effective Psychotherapy With Borderline Patients*. New York, Macmillan, 1987
22. Elkin I, Parloff MB, Hadley SW, et al: NIMH Treatment of Depression Collaborative Research Program: background and research plan. *Arch Gen Psychiatry* 1985; 42:305–316

APPENDIX 1. Item Composition of Psychotherapy Outcome Clusters

COGNITIVE DISORGANIZATION

Psychiatric Status Schedule speech disorganization
 Psychiatric Status Schedule disorientation-memory
 Inpatient Multidimensional Psychiatric Scale (IMPS) conceptual disorganization
 WAIS vocabulary scatter: performance negative
 WAIS vocabulary scatter: verbal negative

PRIMARY PROCESS THINKING

Rorschach percent of primary process responses
 Rorschach density
 Rorschach mean defense demand
 Rorschach content level 1
 Rorschach formal level 1
 Rorschach primary process level 1

DENIAL OF ILLNESS

Psychiatric Status Schedule denial of illness
IMPS anxiety-intropunitiveness
Camarillo Dynamic Assessment Scale: insight
Camarillo Dynamic Assessment Scale: motivation

EGO WEAKNESS

Camarillo Dynamic Assessment Scale: ego strength
Camarillo Dynamic Assessment Scale: sense of personal identity

POSITIVE ATTITUDE

Soskis Attitude Toward Illness Questionnaire: positive
Soskis Attitude Toward Illness Questionnaire: integrates
Soskis Attitude Toward Illness Questionnaire: insight positive
Soskis Attitude Toward Illness Questionnaire: future positive

GLOBAL PSYCHOPATHOLOGY

Menninger Health-Sickness Rating Scale: total score
Psychiatric Status Schedule total score
IMPS total score
Camarillo Dynamic Assessment Scale: weighted total score
Katz Adjustment Scale—Subject: symptom discomfort
Katz Adjustment Scale—Relative: general psychopathology

ANXIETY-DEPRESSION

Psychiatric Status Schedule anxiety-depression

Psychiatric Status Schedule suicide and/or self-mutilation
Psychiatric Status Schedule anxiety
Psychiatric Status Schedule depression-suicide
Psychiatric Status Schedule guilt
Psychiatric Status Schedule phobias
IMPS anxiety-intropunitiveness

RETARDATION-APATHY

Psychiatric Status Schedule retardation
Psychiatric Status Schedule lack of emotion
Psychiatric Status Schedule psychomotor retardation
Psychiatric Status Schedule social isolation
IMPS retardation-apathy
Camarillo Dynamic Assessment Scale: affective contact

SOCIAL DYSFUNCTION

Psychiatric Status Schedule social isolation
Psychiatric Status Schedule daily routine
Psychiatric Status Schedule summary role
Camarillo Dynamic Assessment Scale: object relations
Katz Adjustment Scale—Subject: performance of socially expected activities
Katz Adjustment Scale—Subject: performance of leisure activities
Katz Adjustment Scale—Relative: withdrawal
Katz Adjustment Scale—Relative: performance of socially expected activities
Katz Adjustment Scale—Relative: performance of leisure activities

Aberrant T Cell-Mediated Immunity in Untreated Schizophrenic Patients: Deficient Interleukin-2 Production

Françoise Villemain, M.D., Lucienne Chatenoud, M.D., Ph.D.,
André Galinowski, M.D., Françoise Homo-Delarche, M.D., Ph.D.,
Daniel Ginestet, M.D., Henri Loo, M.D., Edouard Zarifian, M.D.,
and Jean-François Bach, M.D., D.Sc.

The authors examined the immune status at the cellular and humoral levels of 16 untreated schizophrenic patients. No abnormality in the distribution of T cell subsets (CD4⁺, CD8⁺) was detected. The proliferative response to the T cell mitogen phytohemagglutinin was normal. No increase in the number of T cells showing activation markers, such as human leukocyte antigens and interleukin-2 receptors, was noted. Conversely, function studies revealed a clear deficiency in interleukin-2 production by purified T cells. This lower production was probably intrinsic to the patients' T cells, since interleukin-2 production showed normal sensitivity to prostaglandin E₂-mediated down-regulation by autologous monocytes.

(Am J Psychiatry 1989; 146:609-616)

Over the past few years, evidence that schizophrenic patients have abnormal immune reactivity has accumulated. These patients have shown alterations of nonspecific cellular immune parameters, namely, a smaller number of peripheral blood lymphocytes (1-5) as well as an abnormally low capacity of these lymphocytes to respond to normal mitogenic stimuli by proliferation (2) and production of interleukin-2 (6). Moreover, there have been reports describing aberrant cellular and humoral immune reactivity to nerve tissue. Abnormal, in vivo, delayed-type hypersensitivity reactions to crude antigenic preparations (7, 8) and the presence of antibrain antibodies (9-11) have been reported in some schizophrenic patients. Taken together, these data suggest that a primitive or secondary autoimmune process occurs in schizophre-

nia and, more hypothetically, that this process could contribute to the pathogenesis of the disease.

The interpretation of these data is hampered, however, by the fact that most of the patients studied were receiving neuroleptic drugs, which could themselves induce iatrogenic immunomodulation. The aim of this study was to analyze in a group of never-treated schizophrenic patients several immune parameters previously shown to be altered in schizophrenic patients receiving neuroleptic drugs. Particular emphasis was given to the study of interleukin-2 production by stimulated peripheral T lymphocytes and its down-regulation by autologous monocytes. The distribution of the main peripheral regulatory T lymphocyte subsets, namely, helper/inducer (CD4⁺) and cytotoxic/suppressor (CD8⁺) cells, was also studied by using specific mouse monoclonal antibodies. Other monoclonal antibodies were used to detect the presence of peripheral T cells showing phenotypic signs of cell activation, that is, human leukocyte antigen (HLA) class II (DR) antigens and interleukin-2 receptors, which have been observed in abnormal numbers in several autoimmune diseases (12, 13). Finally, we sought the presence in the patients' serum of various non-organ-specific autoantibodies, including anti-T cell autoantibodies. Such autoantibodies have been described in several autoimmune diseases (14, 15) as well as in neuroleptic-treated schizophrenic patients (16).

METHOD

Sixteen schizophrenic patients were included in the present study. All were free of acute or chronic systemic diseases known to be associated with immunological abnormalities. None was receiving any drug at the time of the study, and none had been treated with drugs before the study began. All tests were performed before antipsychotic treatment was started. Informal consent was obtained from the patients after the procedure had been fully explained. Ten age- and sex-matched healthy volunteers were studied as control subjects.

The patients were divided into three groups defined

Received May 23, 1988; revision received Oct. 20, 1988; accepted Nov. 3, 1988. From Hôpital Necker and Hôpital Sainte-Anne, Paris; Hôpital Paul Brousse, Villejuif; and Centre Esquirol, Caen, France. Address reprint requests to Dr. Villemain, INSERM U25, Hôpital Necker, 161, rue de Sèvres, 75015 Paris, France.

Supported by grant CAR.850029 from the Réseau de Recherche Clinique, INSERM.

The authors thank Miss I. Thouard and Mrs. J. Geng for technical assistance and Dr. F. Chaouloff for advice on statistical methods.

Copyright © 1989 American Psychiatric Association.

according to *DSM-III* criteria: group 1, six patients (two male and four female; mean \pm SD age=27.5 \pm 8.1 years, range=18–37 years) with paranoid schizophrenia; group 2, seven patients (five male and two female; age=25.0 \pm 2.5 years, range=21–28 years) with disorganized schizophrenia; and group 3, three patients (two male and one female; age=28.3 \pm 3.0 years, range=25–31 years) with undifferentiated schizophrenia. Seven of the 16 patients were included in the study at the time of their first episodes of the disease; one of these patients had an acute onset, whereas the other six exhibited a more gradual course. The duration of illness ranged from 6 months to 18 years (mean=5 years and 6 months). Nine patients were currently working and seven were unemployed. Eleven patients were unmarried, four were separated, and only one was married at the time of the study. Finally, 12 of the 16 patients did not have family psychiatric histories; the other four had family histories that included various psychiatric disorders.

Thirty milliliters of heparinized peripheral venous blood were collected from each patient and control subject and centrifuged (30 minutes at 400 g) on a Ficoll Paque gradient (Pharmacia, Uppsala, Sweden). Mononuclear cells were recovered at the interface, washed twice in RPMI 1640 medium (GIBCO, Paisley, Scotland), and diluted to 10×10^6 cells/ml. When needed, T lymphocytes were purified by means of E rosetting with the use of neuraminidase-treated sheep red blood cells (for formation of E rosettes) according to a technique already described (12). The rosetting E^+ cell sample thus obtained contained 92%–95% OKT3 $^+$ T cells, whereas the nonrosetting E^- non-T cell sample contained 2%–5% OKT3 $^+$ cells (OKT3 is a mouse monoclonal antibody specific for all mature human T cells), 45%–50% B cells, and 43%–47% monocytes.

T cell subset phenotype was studied, as already described elsewhere (17), by indirect immunofluorescence with the use of the following mouse monoclonal antibodies that recognize differentiation or activation membrane markers: OKT3 (Ortho, Raritan, N.J.), specific for all mature human T cells (anti-CD3); OKT4 (Ortho), specific for helper/inducer T cells (anti-CD4); OKT8 (Ortho), specific for suppressor/cytotoxic T cells (anti-CD8); IOT14 (Immunotech, Marseille, France), specific for the interleukin-2 receptor; and 2.06 (donated by Dr. D. Charron), directed against monomorphic determinants of human HLA class II molecules. The cells (10×10^6 /ml) were incubated at 4 °C with appropriate dilutions of the monoclonal antibodies. After two washes in cold Hanks' balanced salt solution (Eurobio, Paris, France) containing 5% fetal calf serum (GIBCO) and 0.2% sodium azide, the cells were labeled with fluorescein-labeled goat antimouse immunoglobulin G (IgG) antiserum (Nordic, Tilburg, The Netherlands). Following washing and resuspension, one drop was examined under a Leitz Dialux microscope equipped for epifluorescence, and 200 cells per slide were counted.

The percentage of each T cell subset relative to the total number of OKT3 $^+$ cells counted was then calculated, and the ratio of the percentage of OKT4 $^+$ to the percentage of OKT8 $^+$ cells was computed.

The culture medium was RPMI 1640 supplemented with penicillin (100 U/ml), streptomycin (100 mg/ml), 1% L-glutamine (Sigma, St. Louis, Mo.), and fetal calf serum at 2% and 10% final concentration for lymphokine production and cell proliferation, respectively. Mitogen-induced proliferation was tested by stimulating rosetting T cells (E^+ cells, 1×10^6 cells/ml) in flat-bottomed culture microplates (Falcon, Becton Dickinson, Lincoln Park, N.J.), 200 μ l per microwell in triplicate, with phytohemagglutinin A (PHA) (Pharmacia) at a 2- μ g/ml final concentration. Following 48 hours of culture at 37 °C in a 5% CO₂ humidified atmosphere, proliferation was assessed by means of 18 hours of [³H]thymidine (Amersham, Les Ulis, France) (1 μ Ci per well) incorporation. Cells were harvested, and the radioactivity incorporated by each microwell was counted in a Delta 300 microbeta scintillation counter (Searle Analytic, Des Plaines, Ill.). The proliferation index was calculated as follows (cpm=counts per minute):

$$\frac{\text{cpm (cells+PHA)} - \text{cpm (cells-PHA)}}{\text{cpm (cells-PHA)}}$$

To study lymphokine production, rosetting T cells (1×10^6 cells/ml) were stimulated in 24-well Limbro culture plates (GIBCO) (1 ml per well) with PHA at 0.4 μ g/ml and 4.0 μ g/ml final concentrations. Culture supernatants were collected after 48 hours of culture, centrifuged for 10 minutes at 400 g, filtered through 0.45- μ m filters (Millipore, Bedford, Mass.), and stored at -20 °C until tested for interleukin-2 activity. In parallel with cultures that had rosetting E^+ T cells alone, other cultures were made in separate wells, where variable proportions (10% and 30%) of non-rosetting E^- cells were added to the E^+ cell suspensions and stimulated as described. To test the effect of irradiation on interleukin-2 production, cultures of irradiated (1000 rad) E^+ -rosetting T cells were also analyzed.

Interleukin-2 activity contained in culture supernatants was measured in parallel by a biological assay in which the interleukin-2-dependent mouse T cell line CTLL-2 was used and by soluble-phase radioimmunoassay in which human [¹²⁵I]interleukin-2 was used. For the biological assay, CTLL-2 cells diluted at 4×10^3 cells/ml in RPMI 1640 medium supplemented with 10% fetal calf serum, 1% L-glutamine, antibiotics, and 5×10^{-5} M mercaptoethanol were cultured in round-bottomed microplates (Nunc, Roskilde, Denmark) in the presence of serial dilutions of test supernatants. Proliferation was assessed after 72 hours of culture by means of 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Sigma) incorporation. Ten microliters of MTT per microwell

were incubated for 4 hours at 37 °C. Then, to stop the reaction, 150 µl of isopropanol were added to each microwell. The optical density was read in a Multiscan (Dynatech, Marnes La Coquette, France) at 570 nm. Units were calculated by comparison with the mitogenic activity of serial dilutions of a reference supernatant containing, by definition, 1 U/ml of interleukin-2 (produced by 48 hours of PHA stimulation of normal peripheral blood lymphocytes) (18). The unit concentration of each supernatant was calculated by means of a probit program.

For all patients, soluble-phase radioimmunoassay was performed in parallel with the biological assay. The radioimmunoassay kit, including all the reagents, was provided by Medgenix (Fleurus, Belgium). One hundred microliters of the samples to be tested (in duplicate at serial dilutions) were incubated with 100 µl of rabbit antihuman interleukin-2 polyclonal antiserum for 18–24 hours at room temperature. Then 100 µl of the tracer [¹²⁵I]interleukin-2 were added to each tube and incubated for 4 hours at room temperature. Following the addition of antirabbit γ-globulins diluted in a buffer containing polyethylene glycol, cellulose, and polyoxyethylene sorbitan monolaurate, the samples were centrifuged for 15 minutes at 1500 g. The supernatant was aspirated and the radioactivity of the pellet assessed in a gamma counter (LKB, Paris, France).

The same standards used in the biological assay, namely, the natural interleukin-2-containing supernatant and human recombinant interleukin-2, were used in the radioimmunoassay. The bound radioactivity (i.e., the percentage of [¹²⁵I]interleukin-2 bound) was determined as follows (cpm=counts per minute):

$$B/Bo \times 100 = \frac{\text{cpm (standard or sample)} - \text{cpm (nonspecific)}}{\text{cpm (zero standard)} - \text{cpm (nonspecific)}} \times 100$$

where cpm (nonspecific)=buffer plus tracer and cpm (zero standard)=sample containing 0 U/ml of interleukin-2.

The B/Bo×100 values for each standard point were plotted as a function of the interleukin-2 concentration with the use of semilogarithmic paper. Interleukin-2 concentrations in test samples were then calculated by extrapolation to the standard curve.

The prostaglandin E₂ (PGE₂) concentration in culture supernatants was tested by radioimmunoassay as previously described (19). Prostaglandins were extracted from the supernatants according to a modification of Frölich's technique (20). Aliquots of the suspensions were mixed with acetone (1:2, volume per volume) and centrifuged (5 minutes at 3000 g), and the supernatants were treated with 2 volumes of hexane. After acidification to pH 3.5 with 70% citric acid, the lower phase was mixed with 2 volumes of chloroform. Following agitation at 4 °C overnight, the organic phase was evaporated under nitrogen. After extraction, the prostaglandin-containing fractions were sus-

pended in sodium chloride phosphate buffer, pH 7.4, containing 0.1% sodium azide and 0.1% gelatin. Cross-reactivity of the antiserum (anti-PGE₂ antibodies, Institut Pasteur, France) with 25 various prostaglandins and related compounds was lower than 0.1%, except for PGE₂, for which it was 10%. The concentration of PGE₂ in each supernatant was calculated by means of a probit program, and the results were expressed in picograms per milliliter.

Normal T cells were prepared by E rosetting, as already described. Patients' and control subjects' serum was screened for anti-T cell autoantibodies by using an indirect immunofluorescence assay: 10 µl of test or control serum were incubated for 30 minutes at 4 °C with 0.5×10⁶ normal rosetting E⁺ cells in 50 µl final volume. The cells were then washed twice in Hanks' balanced salt solution containing 0.2% sodium azide and 5% fetal calf serum and incubated with an appropriate dilution of fluorescein-conjugated goat antihuman Ig antiserum (Nordic). Following three washes in Hanks' balanced salt solution supplemented with 0.2% sodium azide and 5% fetal calf serum, the cellular suspension was examined under a Leitz Dialux microscope, and 200 cells per slide were scored. The percentages of fluorescent cells were then calculated.

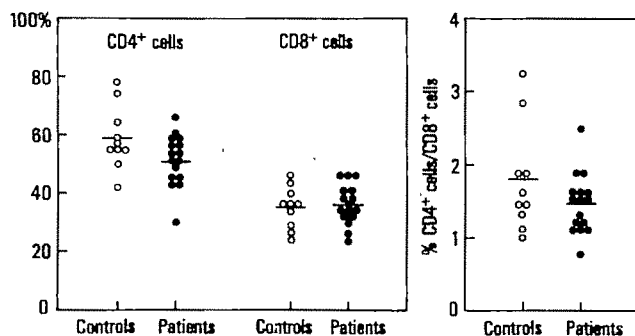
Total antinuclear antibodies were detected in the plasma of the patients and control subjects by means of indirect immunofluorescence assay, as previously described (21). The substrate consisted of 4-µ cryostat sections of mouse liver, flash-frozen in liquid nitrogen, without acetone fixation. The reactant was a fluorescein-conjugated IgG fraction of a goat antihuman Ig serum (IgA, IgG, IgM) (Cappel Laboratories, West Chester, Great Britain). Titers higher than 1/10 were considered positive.

Antihistone antibodies were detected by means of a micro-enzyme-linked immunoabsorbent assay (ELISA) technique, as previously described (22). A positive finding was defined as a difference in optical density (comparing histone-coated plates and noncoated plates for patients) higher than the mean+2 SD for the control subjects' plasma.

Antidenatured DNA antibodies were detected by means of the Farr assay with ¹⁴C-labeled native DNA extracted from *Escherichia coli* (Amersham) and treated at 100 °C for 30 minutes, flash-frozen in ice, and, finally, sonicated, as in a previously described technique (23). A percentage of DNA binding higher than the mean+3 SD in the control subjects' plasma was defined as a positive finding for anti-DNA antibodies.

All of the data we report are expressed as mean±SD. Differences between means were assessed by either two-way analysis of variance followed by post hoc Newman-Keuls q tests (for PGE₂ and interleukin-2 production) or Student's t test for unpaired data (for T cell phenotypes).

Figure 1. T Cell Phenotypes in 16 Schizophrenic Patients and 10 Normal Control Subjects^a



^aNo significant differences between patients and control subjects in percentages of fluorescent cells were found: CD4⁺ cells (mean \pm SD)=51.4% \pm 10.2% for patients and 59.1% \pm 10.6% for normal control subjects; CD8⁺ cells=36.0% \pm 6.5% for patients and 35.1% \pm 7.1% for normal control subjects; ratio of CD4⁺ cells to CD8⁺ cells=1.4% \pm 0.8% for patients and 1.6% \pm 0.6% for normal control subjects.

RESULTS

Peripheral T Cell Differentiation and Activation Markers

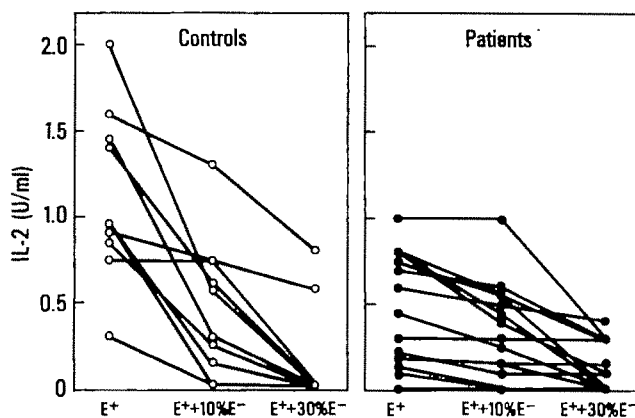
The immunofluorescence assay in which the different mouse monoclonal antibodies were used was performed on E-rosetting T cells. Under these experimental conditions, the mean \pm SD proportion of OKT3⁺ cells including all mature peripheral T lymphocytes was 96.3% \pm 4.5% for the 16 schizophrenic patients and 92.9% \pm 6.9% for the 10 normal control subjects.

As shown in figure 1, a normal distribution of the two main regulatory T cell subsets (i.e., helper/inducer CD4⁺ and cytotoxic/suppressor CD8⁺ T cells) was found in all the schizophrenic patients analyzed. Moreover, none of the patients exhibited any sign of peripheral T cell activation. Thus, similar background percentage values of peripheral T cells showing either HLA class II (DR) antigens or interleukin-2 receptors were found in both schizophrenic patients and normal control subjects without significant statistical difference: mean \pm SD DR⁺ T cells=4.1% \pm 1.3% for the 16 patients and 3.6% \pm 1.3% for the 10 control subjects; mean \pm SD interleukin-2 positive-receptor T cells=0.6% \pm 0.2% for the patients and 0.1% \pm 0.4% for the control subjects.

Mitogen-Induced T Cell Proliferation and Interleukin-2 Production

The capacity of purified E-rosetting T cells to proliferate in the presence of the T-cell-specific mitogen PHA was evaluated for patients and control subjects. Similar proliferation indexes were found for the two groups: mean \pm SD=115.8 \pm 136.7 for the schizophrenic patients (values for 12 patients) and 108.2 \pm 140.6 for the normal control subjects (values for nine

Figure 2. Interleukin-2 (IL-2) Production in 16 Schizophrenic Patients and 10 Normal Control Subjects^a



^aDetected in stimulated T cell culture supernatants by bioassay with the CTLL-2 cell line. When various percentages (10%, 30%) of monocytic cells were added, a significant decrease in T cell interleukin-2 production was observed for normal control subjects and for schizophrenic patients: E⁺ cells (mean \pm SD)=1.10 \pm 0.49 U/ml, E⁺+10% E⁻=0.61 \pm 0.61 U/ml, and E⁺+30% E⁻=0.38 \pm 0.59 U/ml for normal control subjects; E⁺=0.43 \pm 0.33 U/ml, E⁺+10% E⁻=0.35 \pm 0.25 U/ml, and E⁺+30% E⁻=0.17 \pm 0.10 U/ml for schizophrenic patients.

subjects). The difference between mean values was nonsignificant when analyzed by Student's t test.

In parallel with the analysis of the PHA-induced proliferative response, the capacity of mitogen-stimulated T cells to produce interleukin-2 was determined. As shown in figure 2, mean interleukin-2 activity was significantly lower in culture supernatants from the schizophrenic patients than in those from the normal control subjects ($q=5.91$; $p<0.01$); an activity of <0.50 U/ml—close to the background value—was found in nine (56%) of the 16 patients studied. In all patients, interleukin-2 activity was measured in parallel by a biological assay (proliferation of the interleukin-2-dependent CTLL-2 line) and a soluble-phase radioimmunoassay. There was a good correlation of the results obtained with the two tests on the same samples ($r=0.73$, $df=25$, $p<0.01$), which confirmed the absence in these culture supernatants of any soluble material that could have interfered with the biological assay and have accounted for the low interleukin-2 activity values found in a great number of the patients.

To study further the sensitivity of patients' T cells to the mitogenic stimulus, different PHA doses were tested in parallel, with mitogenic (0.4 μ g/ml) and supramitogenic (4.0 μ g/ml) concentrations. Although interleukin-2 production regularly increased with higher mitogen doses, a significant difference was still observed between patients' and control subjects' values according to Student's t test. At the 0.4- μ g/ml mitogen dose, interleukin-2 production (mean \pm SD) was 0.43 \pm 0.33 U/ml for the schizophrenic patients and 1.10 \pm 0.49 U/ml for the control subjects ($t=-4.01$, $df=25$, $p<0.001$). At the 4.0- μ g/ml dose, interleukin-2

production was 2.27 ± 1.22 U/ml for the patients and 4.17 ± 1.99 U/ml for the control subjects ($t = -3.02$, $df = 25$, $p < 0.01$).

The limited number of patients studied does not permit us to draw any conclusion about the possibility of a correlation between the deficit in interleukin-2 production and the clinical form of schizophrenia (paranoid, disorganized, or undifferentiated). It may be noted, however, that the three patients in the study who had undifferentiated schizophrenia showed an interleukin-2 production of < 0.50 U/ml.

Modulation of Interleukin-2 Production by Autologous Non-T Cells and Low-Dose Irradiation

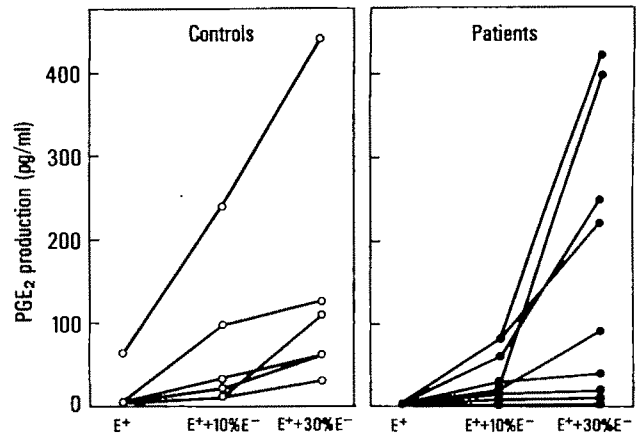
In both patients and normal control subjects, the addition of increasing proportions (10%, 30%) of autologous nonrosetting E^- cells (i.e., a sample including approximately 50% B lymphocytes and 50% monocytes) to the culture resulted in a consistent decrease in T cell interleukin-2 production. For each additional concentration of autologous E^- cells, interleukin-2 production was significantly lower than in culture supernatants of E^+ T cells alone ($F = 9.32$, $df = 2, 72$, $p < 0.001$) (figure 2). In addition, this decrease was found to be significantly more important in schizophrenic patients' T cell cultures ($F = 17.15$, $df = 1, 72$, $p < 0.001$). This pattern was observed even for patients whose T cells alone showed low interleukin-2 production.

It has been reported (24) that the down-regulation of production afforded by autologous non-T cells and, more precisely, by monocytes involves the release of PGE_2 , which in turn activates radiosensitive suppressor T cells. In order to confirm that the inhibition observed in patients and control subjects was mediated by identical pathways, both the PGE_2 concentrations in culture supernatants and the effect of low-dose irradiation of T cells on interleukin-2 production were tested in patients and control subjects.

As shown in figure 3, similar PGE_2 concentrations were found in each given culture condition (i.e., E^+ T cells alone, E^+ T cells plus 10% non-T [E^-] cells, and E^+ T cells plus 30% non-T [E^-] cells) in patients' and control subjects' cellular supernatants. In all cases tested, the increase in PGE_2 values fully paralleled the number of non-T cells present in cell cultures ($F = 7.30$, $df = 2, 19$, $p < 0.01$) without any significant difference between patients and control subjects.

As previously reported, it was found that in both patients and control subjects, low-dose irradiation (1000 rad) of T cells totally overcame the inhibitory effect of PGE_2 on interleukin-2 production, probably through direct action on the suppressor T cell subset that finally mediates down-regulation. Irradiation induced a twofold increase in interleukin-2 production. In each group the increase proportional to the initial interleukin-2 value was such that, even with irradiated T cells, mean interleukin-2 production was significantly lower in the schizophrenic patients than in the

Figure 3. Prostaglandin E_2 (PGE_2) Production in Schizophrenic Patients and Normal Control Subjects*



*The level of PGE_2 increased under the same culture conditions for normal control subjects and for schizophrenic patients, without significant differences: E^+ cells (mean \pm SD) = 12.3 ± 26.6 pg/ml, $E^+ + 10\% E^- = 69.4 \pm 89.4$ pg/ml, and $E^+ + 30\% E^- = 120.8 \pm 178.3$ pg/ml for normal control subjects ($N = 6$); $E^+ = 2.4 \pm 1.6$ pg/ml, $E^+ + 10\% E^- = 35.2 \pm 28.7$ pg/ml, and $E^+ + 30\% E^- = 175.8 \pm 188.1$ pg/ml for schizophrenic patients ($N = 9$).

normal control subjects (mean \pm SD = 1.09 ± 0.60 U/ml for patients and 2.87 ± 1.73 U/ml for control subjects; $t = -3.79$, $df = 24$, $p < 0.001$).

Anti-T Cell Autoantibodies and Antinuclear Autoantibodies

In none of the patients studied was the presence of circulating antibodies reacting with normal T cells detected in the indirect immunofluorescence assay. The difference in the mean \pm SD value of E-rosetting T cells stained with the patients' serum ($1.4\% \pm 2.5\%$) and that of the control patients ($1.2\% \pm 1.5\%$) was nonsignificant.

Five patients (31%) and two control subjects (20%) showed antinuclear antibodies on assessment by indirect immunofluorescence of rat liver tissue sections. Two patients showed considerable concentrations of antidenatured DNA antibodies (17% and 25%). None of the patients exhibited detectable levels of antihistone antibodies.

DISCUSSION

The etiology of schizophrenia is largely unknown. To gain further insight into the pathogenesis of this disease, several hypotheses that involve genetic, biochemical, neurochemical, environmental, and, much more recently, immunological mechanisms (25) have been considered. The theories concerning the involvement of immunological abnormalities in schizophrenia are not recent, since the first studies were published in the 1960s (26–28). More recently, with the develop-

ment of a new research field—neuroimmunomodulation—we can study the relationships between the CNS and the immune system. Thus, the recent data concerning the presence on human lymphocytic cells of receptors for various neurotransmitters (29) has led to a new interest in analyzing the immune status of patients suffering from neurological or psychiatric disorders.

Immune responses are the result of a complex cellular interaction involving functionally and physically distinct lymphocyte subsets together with various soluble mediators produced by either stimulated lymphocytes (i.e., lymphokines) or monocytes (i.e., monokines). In fact, lymphocytes are a heterogeneous group exhibiting either effector or regulatory functions. Among the former one may distinguish Ig-producing B cells and T cells that mediate cytotoxic or delayed-type hypersensitivity reactions. Among the latter are T lymphocytes exhibiting helper/inducer or suppressor functions (17). These various cell subsets may be analyzed by studying not only their functions but also their phenotypes, inasmuch as they show distinct membrane surface antigens or receptors that may be specifically recognized by panels of mouse monoclonal antibodies (17).

Interleukin-2, formerly termed "T cell growth factor," is a glycosylated protein (15-18kDa) produced by T lymphocytes after mitogenic or antigenic stimulation (30). Interleukin-2 has been purified to homogeneity, and its gene has been cloned, making the protein available as recombinant material. Interleukin-2 acts as a growth factor in that it promotes cell proliferation and differentiation of cells exhibiting its specific receptors (31). Originally, interleukin-2 was thought to act exclusively on T cells (mainly cytotoxic T cells and cells mediating delayed-type hypersensitivity reactions) (32), but more recent data have shown that B cells (33) and even monocytes under particular conditions (34) may show interleukin-2 receptors that render these cells sensitive to the lymphokine action.

Our preliminary report (6) showed that interleukin-2 production by PHA-stimulated peripheral T cells from schizophrenic patients who were either untreated or receiving one neuroleptic drug was significantly lower than that of normal control subjects. These data have now been extended to a larger series of patients, who were drug free at the time of study. The results indicate that the abnormality in interleukin-2 production is directly related to the disorder rather than representing an epiphenomenon secondary to drug therapy. It is noteworthy that highly similar results were obtained by using in parallel the conventional biological assay based on the proliferation of the mouse cytotoxic CTLL-2 line and a recently developed soluble-phase radioimmunoassay that uses radiolabeled human interleukin-2 as a tracer. This excludes the possibility that the defect observed in schizophrenia is related to the presence of a soluble material present in the culture supernatants which could interfere with the biological assay. Moreover, the fact that the abnormality in interleukin-2 production in schizophrenia is ob-

served when supramitogenic concentrations of the mitogen are used obviates the possibility that the observed defect is due to an abnormal refractoriness of patients' T lymphocytes to the stimulus.

A decrease in interleukin-2 production can be related either to an intrinsic abnormality of the interleukin-2-producing T cell or to an aberrant regulation of lymphokine production. To gain further insight into these possibilities, parameters of the regulatory pathways of interleukin-2 production were explored. Interleukin-2 production depends closely on the presence of a minimal number of monocytes. On the one hand, monocytes positively modulate interleukin-2 production through the release of interleukin-1 (24). On the other hand, monocytes down-regulate interleukin-2 production by means of the release of prostaglandins (mainly PGE₂) (24). PGE₂ depresses interleukin-2 production by activating radiosensitive specific suppressor T lymphocytes that inhibit the interleukin-2-producing T cells. Studies of *in vitro* induction of suppressor cells by PGE₂ have shown that the suppressor precursors segregate principally with CD8⁺ T cells and, to a lesser degree, with CD4⁺ lymphocytes (35). However, once differentiated, the suppressor effector cell shows only the CD8 phenotype (35).

Results obtained in this study show that for all of the schizophrenic patients studied, the addition of increasing proportions of autologous monocytes induced, as it did for normal control subjects, a significant decrease in interleukin-2 production. Moreover, the analysis of PGE₂ levels in the same culture supernatants that were tested for their interleukin-2 activity did not reveal any significant difference between patients and control subjects. One may thus conclude that the lower interleukin-2 activity observed in schizophrenic patients is not related to abnormally high monocyte activity resulting in increased PGE₂ secretion.

This interpretation is compatible with the observation that lower interleukin-2 production is still observed in cultures from schizophrenic patients after lymphocyte irradiation, which inactivates the radiosensitive suppressor T cells activated by PGE₂. Finally, one may conclude that in schizophrenic patients, lower interleukin-2 activity is more probably related to an intrinsic defect (either qualitative or quantitative) of the interleukin-2-producing T cell than to aberrant regulation of lymphokine production, that is, greater suppression. It is interesting to note that the PHA-induced proliferation of schizophrenic patients' T cells was normal despite the defective interleukin-2 activity (interleukin-2 is one major mediator of PHA-driven proliferation). Such apparently paradoxical results have frequently been observed in various pathological situations, probably because, at least in bulk cultures, more sensitive evaluation of minor or moderate differences is provided by mitogen-promoted interleukin-2 production than by proliferation. Detailed analysis of the proportions of the main peripheral regulatory T cell subsets—helper/inducer (CD4⁺) and

cytotoxic/suppressor ($CD8^+$)—revealed no numerical abnormality for any of the schizophrenic patients. These results underline the fact that functional T cell abnormalities do not necessarily correlate with major numerical imbalances.

Lower interleukin-2 production similar to that described here has been reported in experimental animals as well as in humans with autoimmune diseases (36). These findings, added to some reports suggesting the presence of autoantibodies directed to nerve tissue in schizophrenic patients, prompted us to look for other parameters of immunity known to be altered in ongoing autoimmune processes, i.e., the presence of antinuclear (37) or anti-T cell autoantibodies (14) and of circulating activated T cells (38–43).

In vivo activated T cells show class II HLA antigens and/or interleukin-2 receptors that may be characterized by means of specific monoclonal antibodies. High proportions of DR^+ T cells have been reported in a number of autoimmune disorders, including systemic lupus erythematosus (38), rheumatoid arthritis (39), type I insulin-dependent diabetes (40), Graves' disease (41), Hashimoto's thyroiditis (42), and Addison's disease (43). However, in none of the schizophrenic patients we studied could any phenotypical sign of T cell activation be found. This finding is at variance with previous reports by Hirata-Hibi et al. (44, 45), but it must be stressed that these authors used cytological criteria (clear cytoplasmic basophilia and irregular nuclear shape, often showing a lobulation or deep indentation) to characterize the "activated" P cells they described. However, in the present study we used membrane labeling with monoclonal antibodies recognizing membrane antigens that are exhibited exclusively by activated cells. The difference in techniques may well explain the discrepancy between our results and those obtained by Hirata-Hibi et al.

Anti-T cell autoantibodies are found in several autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis (46). Here again, however, the serum from the schizophrenic patients we studied did not show any abnormal anti-T cell reactivity.

Finally, some antinuclear autoantibodies, including antidenatured DNA and antihistone antibodies, were present in our series of untreated schizophrenic patients: two patients showed positive titers of antidenatured DNA antibodies. Further analysis of a larger group of patients would be needed to confirm this finding and draw firm conclusions about the significance of these autoantibodies in schizophrenia. It must be stressed that this result is not necessarily in opposition to various reports, including one of ours (16), of high titers of antinuclear autoantibodies in patients with schizophrenia or affective disorders. In fact, all of these reports, which are at variance with the findings of the present study, concerned patients receiving combinations of neuroleptic, thymoregulator, and anxiolytic drugs. Thus, it appears that the presence of antinuclear antibodies, rather than representing a hallmark of

these disorders, is an epiphenomenon related to the therapy received by these patients. This interpretation is further strengthened by the fact that, at least in our previous study (16), mainly antihistone antibodies were found. This is precisely the type of antinuclear antibody most commonly found in drug-induced lupus syndromes (47).

CONCLUSIONS

The present study confirms and extends for the first time in a series of never-treated schizophrenic patients preliminary data showing that abnormal interleukin-2 production is associated with schizophrenia. At present it is difficult to ascertain whether this defect reflects CNS abnormalities. Given the rapidly growing evidence on the interactions that exist between the CNS and the immune system, the present findings further stress the importance of developing collaborative CNS and immune system studies of psychiatric patients to better define whether the CNS plays a role in the abnormalities observed.

It is still impossible to ascertain whether this abnormality is correlated with any particular clinical form of schizophrenia (paranoid, disorganized, or undifferentiated). A study in progress, which includes larger numbers of patients in each clinically defined group, will probably resolve this important question and better establish the possible relationship between the abnormality of T cell function and the pathogenesis of schizophrenia.

REFERENCES

1. Loseva TM: Thymus dependent lymphocytes in the spontaneous rosette-formation reaction in schizophrenia. *Zh Nevropatol Psikhiatr* 1977; 77:692–695
2. Vartanian ME, Kolyskina GJ, Lozovsky DV, et al: Aspects of humoral and cellular immunity in schizophrenia. *Birth Defects* 1978; 5:339–364
3. Duorakova M, Zuolsky P, Lundre H: Endogenous psychoses and T and B lymphocytes. *Folia Haematol (Leipz)* 1980; 107:221–228
4. Nyland H, Naess A, Lundre H: Lymphocyte subpopulations in peripheral blood from schizophrenic patients. *Acta Psychiatr Scand* 1980; 61:313–318
5. Coffey CE, Sullivan JL, Rice JR: T lymphocytes in schizophrenia. *Biol Psychiatry* 1983; 18:113–119
6. Villemain F, Chatenoud L, Guilibert E, et al: Decreased production of interleukin-2 in schizophrenia. *Ann NY Acad Sci* 1987; 496:669–675
7. Jankovic BD, Jakulic S, Horvat J: Schizophrenia and other psychiatric diseases: evidence for neurotissue hypersensitivity. *Clin Exp Immunol* 1980; 40:515–522
8. Jankovic BD: Neural tissue hypersensitivity in psychiatric disorders with immunologic features. *J Immunol* 1985; 135:853s–857s
9. Baron M, Stern M, Anavi R, et al: Tissue-binding factor in schizophrenic sera: a clinical and genetic study. *Biol Psychiatry* 1977; 12:199–219
10. Heath RG: An antibrain globulin, in *Biochemistry, Schizophrenia and Affective Illnesses*. Edited by Himwich HW. Baltimore, Williams & Wilkins, 1970
11. Ganguli R, Rabin BS, Kelly RH, et al: Clinical and laboratory

- evidence of autoimmunity in acute schizophrenia. *Ann NY Acad Sci* 1987; 496:676-685
12. Chatenoud L, Dugas B, Beaurain G, et al: Presence of preactivated T cells in hemodialyzed patients: their possible role in altered immunity. *Proc Natl Acad Sci USA* 1986; 93:7457-7461
 13. Jackson RA, Morris MA, Haynes BF, et al: Increased circulating Ia-antigen-bearing T cells in type I diabetes mellitus. *N Engl J Med* 1982; 306:785-788
 14. Yamada A, Cohen PL, Winfield JB: Subset specificity of anti-lymphocyte antibodies in systemic lupus erythematosus: preferential reactivity with cells bearing the T4 and autologous erythrocyte receptor phenotypes. *Arthritis Rheum* 1985; 28:262-270
 15. Williams RC Jr, Lies RB, Messner RP: Inhibition of mixed leukocyte culture responses by serum and γ -globulin fractions from certain patients with connective tissue disorders. *Arthritis Rheum* 1973; 16:597-605
 16. Villemain F, Magnin M, Feuillet-Fieux NM, et al: Antihistone antibodies in schizophrenia and affective disorders. *Psychiatry Res* 1988; 24:53-60
 17. Kung PC, Goldstein G, Reinherz EL, et al: Monoclonal antibodies defining distinctive human T cell surface antigens. *Science* 1979; 206:347-349
 18. Bertoglio J, Boisson N, Bonnet MC, et al: First French workshop on standardization of human IL-2: joint report. *Lymphokine News* 1982; 1:121-127
 19. Dray F, Charbonnel B, Maclof J: Radioimmunoassay of prostaglandins F₂, E₁ and E₂ in human plasma. *Eur J Clin Invest* 1975; 5:311-318
 20. Papiernik M, Homo-Delarche F: Thymic reticulum in mice, III: phagocytic cells of the thymic reticulum in culture secrete both prostaglandin E₂ and interleukin 1 which regulate thymocyte proliferation. *Eur J Immunol* 1983; 13:689-692
 21. Tan EM: Relationship of nuclear staining patterns with precipitating antibodies in systemic lupus erythematosus. *J Lab Clin Med* 1967; 70:800-812
 22. Quérin S, Feuillet-Fieux MN, Jacob L, et al: Specificity of acetabulol-induced antinuclear antibodies. *J Immunopharmacol* 1986; 8:633-649
 23. Pincus T, Schur PH, Rose JA, et al: Measurement of serum DNA binding activity in systemic lupus erythematosus. *N Engl J Med* 1969; 281:701-705
 24. Chouaib S, Chatenoud L, Klatzmann D, et al: The mechanism of inhibition of human IL-2 production, II: PGE₂ induction of suppressor T lymphocytes. *J Immunol* 1984; 132:1851-1857
 25. De Lisi LE: Is immune dysfunction associated with schizophrenia? a review of the data. *Psychopharmacol Bull* 1984; 20:509-513
 26. Fessel WJ: Autoimmunity and mental illness. *Arch Gen Psychiatry* 1962; 6:320-324
 27. Fessel WJ: The "antibrain" factors in psychiatric patients' sera. *Arch Gen Psychiatry* 1963; 8:614-622
 28. Heath RG, Krupp IM: Schizophrenia as an immunologic disorder, I: demonstration of antibrain globulins by fluorescent antibody techniques. *Arch Gen Psychiatry* 1967; 16:1-9
 29. Tecoma ES, Leighton LY: Psychic distress and the immune response. *Life Sci* 1985; 36:1799-1812
 30. Watson J, Mochizuki D: Interleukin-2: a class of T cell growth factor. *Immunol Rev* 1980; 51:257-278
 31. Fletcher M, Goldstein AL: Recent advances in the understanding of the biochemistry and clinical pharmacology of interleukin-2. *Lymphokine Res* 1987; 1:45-57
 32. Morgan-DA, Ruscetti FW, Gallo RC: Selective in vitro growth of T lymphocytes from normal human bone marrows. *Science* 1976; 193:1007-1008
 33. Tsudo M, Ichiyama T, Uchino H: Expression of Tac antigen on activated normal human B cells. *J Exp Med* 1984; 160:612-617
 34. Malkovsky M, Loveland B, North M, et al: Recombinant interleukin-2 directly augments the cytotoxicity of human monocytes. *Nature* 1987; 325:262-265
 35. Chouaib S, Fradelizi D: The mechanism inhibition of human interleukin-2 production. *J Immunol* 1982; 129:2463-2468
 36. Alcocer-Varela J, Alarcón-Segovia D: Decreased production of and response to interleukin-2 by cultured lymphocytes from patients with systemic lupus erythematosus. *J Clin Invest* 1982; 69:1388-1392
 37. Decker JL, Steinberg AD, Reinertsen JL, et al: Systemic lupus erythematosus: evolving concepts. *Ann Intern Med* 1979; 91:587-604
 38. Koide J: Functional property of Ia-positive T cells in peripheral blood from patients with systemic lupus erythematosus. *Scand J Immunol* 1985; 22:577-584
 39. Winchester RJ, Kunkel HG: The human Ia system. *Adv Immunol* 1979; 28:221-226
 40. Alviggi L, Johnston C, Hoskins PJ, et al: Pathogenesis of insulin-dependent diabetes: a role for activated T lymphocytes. *Lancet* 1984; 2:4-5
 41. Jackson RA, Haynes BF, Buroh WM, et al: Ia⁺ T cells in new onset Graves' disease. *J Clin Endocrinol Metab* 1984; 59:187-190
 42. Canonica GW, Bagnasco M, Cate G, et al: Circulating T lymphocytes in Hashimoto's disease: imbalance of subsets and presence of activated cells. *Clin Immunol Immunopathol* 1982; 23:616-625
 43. Rabinowe SL, Jackson RA, Dluhy RG, et al: Ia-positive T lymphocytes in recently diagnosed idiopathic Addison's disease. *Am J Med* 1984; 77:597-601
 44. Hirata-Hibi M, Higashi S, Tachibana T, et al: Stimulated lymphocytes in schizophrenia. *Arch Gen Psychiatry* 1982; 39:82-87
 45. Hirata-Hibi M: Evidence of lymphocyte abnormality in schizophrenia, in *Viruses, Immunity and Mental Disorders*. Edited by Kurstak E, Lipowski ZJ, Morozov PV. New York, Plenum, 1987
 46. Robbins WC, Holman HR, Deicher HR, et al: Complement fixation with cell nuclei and DNA in lupus erythematosus. *Proc Soc Exp Biol Med* 1957; 96:575-578
 47. Weinstein A: Lupus syndromes induced by drugs, in *The Clinical Management of Systemic Lupus Erythematosus*. Edited by Schur PH. Boston, Grune & Stratton, 1983

Double-Blind Controlled Trial Comparing Carbamazepine to Oxazepam Treatment of Alcohol Withdrawal

Robert Malcolm, M.D., James C. Ballenger, M.D.,
Ellie T. Sturgis, Ph.D., and Raymond Anton, M.D.

Of 86 alcoholic men with severe alcohol withdrawal who began a double-blind controlled study comparing carbamazepine, 800 mg/day, to oxazepam, 120 mg/day, 66 (carbamazepine, N=32; oxazepam, N=34) completed the 7-day trial. In general, the drugs were found to be equally efficacious in treating the withdrawal syndrome and not significantly different with respect to side effects. The subjects taking oxazepam had an increase in global psychological distress from day 3 to day 7, and those taking carbamazepine exhibited a decline. The study suggests that carbamazepine is as effective and safe as benzodiazepine treatment for alcohol withdrawal.

(Am J Psychiatry 1989; 146:617-621)

Despite 200 years of observation and treatment of alcoholism (1), the pathophysiology of alcohol withdrawal states remains unknown. Sellers and Kalant (2) have postulated that tolerance to and physical dependence on ethanol lead to neurophysiologic changes in the CNS that compensate for the depressant effects on neuronal excitability, impulse conduction, and neurotransmitter functions. When alcohol is reduced or removed, these adaptations immediately become pathologic and produce changes indicating a hyperexcitable state in the CNS. Ballenger and Post (3) have suggested that limbic system kindling may be the neuropathologic mechanism causing repeated withdrawal states to become increasingly severe over time. Such kindling-induced CNS changes could be responsible for the behavioral, cognitive, affective, and even psychotic manifestations and seizures that occur in the later stages of alcoholism.

Received Feb. 5, 1988; revisions received June 20 and Oct. 20, 1988; accepted Oct. 27, 1988. From the Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, and the VA Medical Center, Charleston, S.C. Address reprint requests to Dr. Malcolm, Department of Psychiatry and Behavioral Sciences, MUSC Medical Center, 171 Ashley Ave., Charleston, SC 29425-0742.

Supported by VA research funds.

Carbamazepine and identically appearing placebo were supplied by Ciba-Geigy Pharmaceuticals; oxazepam and identically appearing placebo were supplied by the hospital pharmacy.

Carbamazepine is an iminostilbene derivative that resembles the tricyclic antidepressant imipramine. Until its introduction into psychiatry (4, 5), carbamazepine was primarily used for neurologic indications, e.g., in the treatment of trigeminal neuralgia, other pain syndromes, and epilepsy. We became interested in its potential use in alcoholism and alcohol withdrawal because of its ability to both retard the development of kindling and suppress established kindled foci. We had hypothesized on theoretical and clinical grounds that a kindling-like process might be responsible for the progressive increase of withdrawal symptoms and psychiatric difficulties in alcoholics who had undergone alcohol withdrawal several times, and that carbamazepine would retard such a kindling-like process and lead to improvement in withdrawal-related symptoms and in the course of an individual's alcoholism (3).

At least 135 different drugs and drug combinations have been described in the literature for the treatment of alcohol withdrawal states (2). Moskowitz et al. (6) reviewed 80 clinical trials of pharmacologic treatment of alcohol withdrawal and evaluated 29 double-blind controlled trials in detail; they concluded that the benzodiazepines are more efficacious and safer than other classes of drugs but that no one benzodiazepine appears to be the most effective when examined in group studies. In the United States, benzodiazepines have become the standard therapy for alcohol withdrawal states. In Europe and the United Kingdom, the treatment of alcohol withdrawal states has remained more diverse, and carbamazepine has become increasingly popular in such treatment. Open trials with carbamazepine have demonstrated its effectiveness and even potential superiority over other agents in the management of alcohol withdrawal states (7, 8). Four double-blind, controlled studies of carbamazepine treatment of alcohol withdrawal (9-12) reported that carbamazepine was superior to placebo in the treatment of withdrawing alcoholics and was equal to barbitol, tiapride, and clomethiazole in efficacy. There is some evidence that it may be somewhat superior to other drugs in terms of rapidity of amelioration of withdrawal symptoms and in the reduction of associated psychiatric symptoms (11).

We, and others (3, 13, 14), have suggested that anticonvulsants with antikindling properties may be supe-

rior to traditional benzodiazepines in preventing alcohol withdrawal seizures and in potentially reducing long-term neurologic, behavioral, and psychiatric complications of alcoholism. To our knowledge, no double-blind, controlled studies have directly compared carbamazepine to a benzodiazepine in the treatment of alcohol withdrawal. Therefore, we conducted a 7-day, double-blind, parallel controlled trial of carbamazepine versus oxazepam in the treatment of moderate to severe alcohol withdrawal in hospitalized alcoholics to compare the relative efficacy of the two drugs in the management of alcohol withdrawal.

METHOD

The Alcohol and Drug Treatment Program unit of the Veterans Administration Medical Center, Charleston, S.C., has an average of 540 admissions per year, and approximately 20% of the patients require pharmacological treatment for symptoms of primary alcohol withdrawal. All of the 512 daytime admissions to the unit during the 20-month period of study were screened for inclusion in the study. In order to participate in the study, patients had to be men between the ages of 18–65 years, meet the *DSM-III* criteria for alcohol dependency, be able to give informed consent, have a Mini-Mental State (15) score above 25, and have an admission score on the Clinical Institute Withdrawal Assessment for Alcohol Scale of 20 or higher, which indicates substantial withdrawal symptoms requiring treatment (16). Our primary exclusion criteria were a history of 1) daily use of CNS active drugs, including prescription, nonprescription, and illicit agents, 2) 5 or more days of illicit drug abuse (other than alcohol) in the 30 days before admission, 3) allergic or adverse reactions to oxazepam or carbamazepine, or 4) manic-depressive illness, schizophrenia, or dementia. Other exclusion criteria included a history of hepatic encephalopathy, jaundice, ascites, diabetes, renal disease, neurologic disease (excluding peripheral neuropathy), or leukopenia. Secondary exclusion criteria that applied from day 1 to day 3 of the study included liver function transaminase levels (SGOT, LDH, and SGPT) that were 2.5 times higher than normal, a total WBC below 4000/mm³, or a platelet count below 100,000/mm³. Subjects were also excluded if they had participated in any drug research protocol within the preceding 12 months.

Of the 512 potential subjects, 426 (83%) failed to meet study criteria (205 or 40% because of low alcohol withdrawal scale scores), and 86 (17%) met initial study criteria and gave informed consent to participate. The 86 subjects were blindly assigned to a group who received carbamazepine, 200 mg q.i.d. (N=43), or a group who received oxazepam, 30 mg q.i.d. (N=43). Five subjects (four in the carbamazepine group and one in the oxazepam group) were dropped from the study between days 2 and 3 because initial laboratory studies done on the day of admission met

exclusion criteria (hepatic transaminase values 2.5 times higher than normal). Of the 81 remaining subjects (39 in the carbamazepine group, 42 in the oxazepam group), 15 dropped out between days 4 and 7: seven in the carbamazepine group (four against medical advice, one who developed a diffuse rash, one who developed mental confusion, and one who received an additional medication, diazepam, excluded by the protocol) and eight in the oxazepam group (three against medical advice, one who developed a generalized rash, one who developed mental confusion, one who was transferred to surgery, and two who received medications, diazepam and propranolol, excluded by the protocol). Thus, 66 subjects (32 in the carbamazepine group, 34 in the oxazepam group) completed the 7-day trial.

To determine whether the randomization procedure had resulted in equivalent groups at the beginning of the trial, we compared the subjects assigned to the carbamazepine group with those in the oxazepam group with respect to 11 baseline variables: Clinical Institute Withdrawal Assessment for Alcohol Scale score, age, height, weight, education level, age at onset of reported drinking, age at onset of alcohol becoming a problem, age at onset of shakes after termination of drinking, age at onset of delirium tremens (if any), number of arrests for "driving under the influence," and breath alcohol level at admission to the unit.

We assessed symptoms of alcohol withdrawal in five areas for both groups of subjects. 1) Alcohol withdrawal severity was assessed with the Clinical Institute Withdrawal Assessment for Alcohol Scale (16), a standardized and validated withdrawal severity index that rates 15 clinical dimensions, on which scores of less than 10 represent minimal withdrawal symptoms, scores of 10–19 indicate moderate symptoms, and scores of greater than 20 represent substantial symptoms. This scale was administered twice a day, 1 hour after administration of medication. 2) Physiological measures, assessed twice a day, included pulse, blood pressure, and tremor. Tremor was measured in beats per minute (17) by using a Grass model 7 physiograph with an accelerometer transducer attached to a finger of an outstretched hand (Grass Instrument Co., model SPA-1). 3) Neurological measures, also evaluated twice a day, included deep tendon reflexes and a standardized rating of ataxia observed while the subject walked heel to toe for 3 m. Both were rated on a 0- to 4-point scale. 4) Self-report measures included levels of sleepiness, anxiety, alcohol craving, energy, anger, craving for sweets, hunger, shakiness, nausea, need for alcohol, and quality of the previous night's sleep and were rated by each patient on 100-mm visual analog scales once a day in the afternoon. 5) Standard psychological testing included measures of overall psychological distress, depression, anxiety, and mental functioning evaluated at baseline and on days 3 and 7 of treatment. The Global Severity Index of the Symptom Checklist 90-R (SCL-90-R) (18) was used as a standard measure of overall psychological distress. The Beck

TABLE 1. Significant and Nearly Significant Time Effects, Group Effects, and Group by Time Interactions of Outcome and Side Effect Variables for Alcoholic Men Taking Carbamazepine or Oxazepam for Alcohol Withdrawal Symptoms

Analysis and Variable	F	df	Greenhouse-Geisser-Corrected p	Bonferroni-Corrected p
Time effect				
Clinical Institute Withdrawal Assessment for Alcohol Scale	329.4	6, 432	≤0.001	≤0.001
Tremor	81.0	6, 426	≤0.001	≤0.001
Systolic blood pressure	5.3	6, 426	≤0.001	≤0.01
Pulse	3.4	6, 426	≤0.01	≤0.10
Gait	43.1	6, 426	≤0.001	≤0.001
SGOT	5.8	2, 148	≤0.01	≤0.10
WBC	10.5	2, 146	≤0.001	≤0.01
Shakiness	12.3	5, 365	≤0.001	≤0.01
Nervousness	8.3	5, 365	≤0.001	≤0.01
Craving for alcohol	10.9	5, 365	≤0.001	≤0.01
Anger	4.4	5, 360	≤0.01	≤0.05
Beck Depression Inventory	17.1	1, 77	≤0.001	≤0.05
Daytime sleepiness	5.1	5, 365	≤0.001	≤0.05
Lack of energy	10.7	5, 360	≤0.001	≤0.01
Nausea	8.8	5, 360	≤0.001	≤0.01
Group effect				
SCL-90-R global distress score	13.5	1, 59	≤0.001	≤0.05
Group by Time interaction				
Pulse	2.7	6, 426	≤0.01	n.s.
Deep tendon reflex	2.2	6, 426	≤0.10	n.s.
Tremor	2.4	6, 426	≤0.06	n.s.
Anger	2.8	5, 360	≤0.01	n.s.
Wechsler Memory Scale	3.8	1, 63	≤0.06	n.s.
State-Trait Anxiety Inventory, state portion	7.7	1, 63	≤0.01	n.s.

Depression Inventory (19) was used to evaluate depression and mood state. The state portion of the State-Trait Anxiety Inventory (20) was used to assess anxiety. The Wechsler Memory Scale (21) was used to evaluate memory.

Laboratory tests done on days 1, 3, and 7 included CBCs, routine chemistries, liver and thyroid function studies, and carbamazepine levels.

Because of the difference in appearance of carbamazepine and oxazepam, all subjects received a capsule and a tablet every 6 hours (one of active drug and one of placebo) for 7 days. All subjects, research staff, and ward clinical personnel were blind to the study drugs. One investigator (R.A.), who monitored laboratory values but did not participate in the rating of symptoms, was not blind to subject assignment.

A power analysis was performed to determine the sample size needed to detect a 10% difference in group responses given an alpha level of 0.05. With the power of the design set at 80%, it was determined that 80–100 subjects would need to be enrolled, anticipating a 20% dropout rate.

All analyses were done with the BMDP statistical software package. Significance levels were established at the 0.05 level before the study began, and analyses were divided into outcome and side effect data. Treatment groups were compared by means of a repeated measures analysis of variance (ANOVA) for group effects, time effects, and Group by Time interactions. Since all subjects entered the study with approximately the same level of withdrawal symptoms, and since alcohol withdrawal is a self-limiting illness, both groups

were expected to show similar scores at the beginning and at the end of the study. Thus, the Group by Time interactions were considered to be the most valuable analysis in demonstrating which agent acted more rapidly. Since we were evaluating the relative efficacy of the two detoxification agents, two-tailed tests of significance were used and the resultant p values were adjusted by using the Greenhouse-Geisser and Bonferroni correction factors to reduce the likelihood of type 1 error. We report the significant p values from both correction factors in table 1, but the significant findings reported in Results are based on the Bonferroni correction ($p < 0.05$). Demographic variables of the two treatment groups and of the completers and dropouts were compared with Student's t tests.

RESULTS

The treatment groups differed significantly on only one of the 11 baseline variables, the mean \pm SD age of reported symptoms of delirium tremens (carbamazepine, 30.3 ± 4.4 years; oxazepam, 43.4 ± 9.9 years; $t = -4.11$, $df = 18$, $p < 0.001$). Therefore, the two groups were considered to be essentially equivalent at entry to the study. Completers differed significantly from dropouts on two of the 11 baseline variables. Forty-one of the 66 completers and 17 of the 20 dropouts had had at least one arrest for "driving under the influence." These 41 completers had significantly more mean \pm SD lifetime arrests for "driving under the influence" than the 17 dropouts (1.8 ± 1.0 and 1.2 ± 0.4 , respectively;

$t=2.53$, $df=56$, $p<0.02$). The completers also had a significantly higher educational level than the dropouts (11.6 ± 2.3 years and 10.6 ± 2.0 years, respectively; $t=-1.98$, $df=79$, $p<0.05$).

For the 32 remaining patients in the carbamazepine group, carbamazepine serum levels, obtained on days 3 and 7 of the study, were analyzed in the clinical laboratory by means of an immunofluorescent technique (TDX system, Abbott Laboratories). The mean \pm SD carbamazepine level on day 3 (9.8 ± 2.9 kg/ml) was significantly higher than on day 7 (8.5 ± 2.5 kg/ml) ($t=1.76$, $df=62$, $p<0.05$); however, this difference was not considered to be clinically significant.

Table 1 presents the significant and almost significant time effects, group effects, and Group by Time interactions with respect to global alcohol withdrawal assessment, physiologic variables, laboratory values, self-report scales, psychometric scales, and side effects. Both carbamazepine and oxazepam treatments resulted in significant improvement in withdrawal symptoms as measured by the Clinical Institute Withdrawal Assessment for Alcohol Scale. Both treatment groups achieved maximum reduction of symptoms between days 4 and 5, and little clinical change was noted for either group after day 5 (figure 1). There were no significant group effect differences between carbamazepine and oxazepam on this scale.

There were no significant group effect differences between the two drugs with respect to tremor, deep tendon reflexes, gait, blood pressure, and pulse. For both groups, systolic blood pressure showed a significant decline across time, and tremor and gait improved over time.

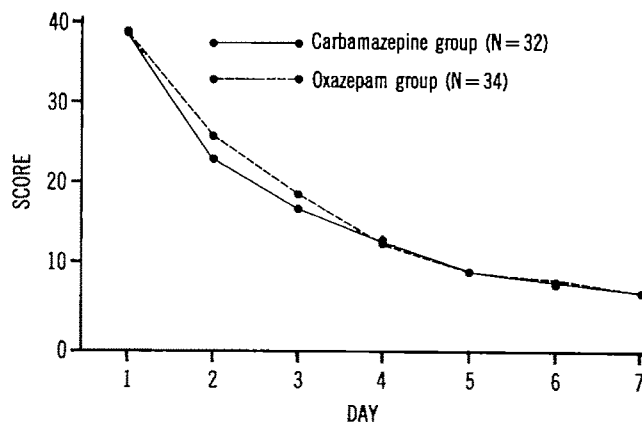
The SGOT, alkaline phosphatase, and platelet values were generally unchanged over the course of the study. Both groups showed a significant decline in WBCs over the course of the study. At baseline, WBCs were approximately $7900/\text{mm}^3$ in both groups; at the end of the study, they averaged $6800/\text{mm}^3$ for the carbamazepine group and $7600/\text{mm}^3$ for the oxazepam group. No patient in either group had a WBC below $4000/\text{mm}^3$.

There were no significant group effect differences between the two drugs on any of the self-report scales. Self-reported shakiness, nervousness, anger, and craving for alcohol significantly improved for both groups over the course of the study.

The group analysis of the global distress score of the SCL-90-R indicated significantly less psychological distress for the carbamazepine group at the end of the study than for the oxazepam group. Mean scores for both groups were equivalent on day 3; however, by day 7, scores for the oxazepam group had increased and scores for the carbamazepine group had declined. Depression scores (Beck scale) improved for both groups over time.

Both medications significantly reduced disturbances of gait, daytime sleepiness, lack of energy, craving for alcohol, and nausea, and there were no significant dif-

FIGURE 1. Scores on the Clinical Institute Withdrawal Assessment for Alcohol Scale for Alcoholic Men in a 7-Day, Double-Blind, Controlled Trial of Carbamazepine Versus Oxazepam



ferences between carbamazepine and oxazepam on these variables.

DISCUSSION

Our results document that carbamazepine is as effective as oxazepam in the treatment of substantial alcohol withdrawal in hospitalized male alcoholics. There were no significant overall differences between carbamazepine and oxazepam in ameliorating the symptoms of alcohol withdrawal measured by our primary assessment of withdrawal symptoms, the Clinical Institute Withdrawal Assessment for Alcohol Scale, and most other symptoms of withdrawal. Both medications were effective and appeared to be roughly equivalent. The subjects' global distress scores on the SCL-90-R indicate that psychiatric symptoms may be more rapidly reduced by carbamazepine than by oxazepam. This potential psychiatric difference between carbamazepine and oxazepam is consistent with previous studies of carbamazepine in alcohol withdrawal (8, 11).

The overall side effect profiles of each drug did not differ significantly. Dropouts due to side effects were low for both the carbamazepine and the oxazepam groups. The carbamazepine group had a mean decline in WBCs of about $1100/\text{mm}^3$, a finding consistent with previous observations (5, 22). This decline was not associated with agranulocytosis (23) or other clinically significant sequelae.

Our results are consistent with evidence from several open and controlled studies from Europe which indicates that carbamazepine is an effective treatment of alcohol withdrawal states (7-12). We did not find advantages of carbamazepine substantial enough to warrant its routine replacement of benzodiazepines in the management of most alcohol withdrawal syndromes; however, we suggest that carbamazepine should be studied further to investigate whether it is more effective than benzodiazepines in ameliorating psychiatric

symptoms of alcohol withdrawal. In addition, carbamazepine may prove to be more useful than oxazepam or other benzodiazepines in the management of alcohol withdrawal states in outpatient settings because it is not a drug of abuse and is not likely to be abused with alcohol.

Several reviews (3, 13, 14) have recommended the use of carbamazepine to treat alcohol withdrawal states because of its specific antikindling effects in limbic structures. If kindling-like changes in limbic areas are involved with alcohol withdrawal symptoms as has been hypothesized (3), then carbamazepine may have specific advantages over other agents. We (24) have observed that individuals who have had five or more alcohol detoxifications appear to have a greater risk for alcohol withdrawal seizures. Also, those individuals who have made multiple attempts at alcohol withdrawal appear to be at greater risk for long-term psychiatric and neurologic sequelae of alcoholism (3). We postulate that if multiple episodes of alcohol withdrawal in chronic alcoholics were treated by carbamazepine, the antikindling effects of carbamazepine could offer protection against the hypothesized cumulative kindling-like changes in the brain; if such changes occur and if they are at least partly involved in the progressive increases in psychiatric and neurologic symptoms in alcoholics, carbamazepine treatment of individual withdrawal episodes might retard this progression. Future studies should be directed at comparisons between carbamazepine and benzodiazepines in alcoholics who have undergone several withdrawal treatments. On the basis of our observation that carbamazepine was more effective than oxazepam in improving psychiatric symptoms, we recommend that carbamazepine be evaluated in the rehabilitation phase of alcoholism treatment.

REFERENCES

1. Romano J: Early contributions to the study of delirium tremens. *Ann Med History (Series III)* 1941; 3:128-138
2. Sellers E, Kalant H: Alcohol intoxication and withdrawal. *N Engl J Med* 1976; 294:757-762
3. Ballenger JC, Post RM: Carbamazepine in alcohol withdrawal syndromes and schizophrenic psychosis. *Psychopharmacol Bull* 1984; 20:572-584
4. Okuma T, Kishimoto A, Inoue K, et al: Anti-manic and prophylactic effects of carbamazepine on manic-depressive psychosis. *Folia Psychiatr Neurol Jpn* 1973; 27:283-297
5. Ballenger JC, Post RM: Carbamazepine in manic-depressive illness: a new treatment. *Am J Psychiatry* 1980; 137:782-790
6. Moskowitz SB, Chalmers TC, Sacks H, et al: Deficiencies of clinical trials of alcohol withdrawal. *Alcoholism (NY)* 1983; 7: 42-46
7. Brune F, Busch H: Anticonvulsant-sedative treatment of delirium alcoholicum. *Q J Stud Alcohol* 1971; 32:334-342
8. Poutanen P: Experience with carbamazepine in the treatment of withdrawal symptoms in alcohol abusers. *Br J Addict* 1979; 74: 201-204
9. Bjorkqvist S, Mekela R, Malinen L: Ambulant treatment of alcohol withdrawal symptoms with carbamazepine: a formal multicenter double-blind comparison with placebo. *Acta Psychiatr Scand* 1976; 53:333-342
10. Ritola E, Malinen L: A double-blind comparison of carbamazepine and clomethiazole in the treatment of alcohol withdrawal syndrome. *Acta Psychiatr Scand* 1981; 64:254-259
11. Agricola R, Mazzanino M, Urani R: Treatment of acute alcohol withdrawal with carbamazepine: a double-blind comparison with tiapride. *J Int Med Res* 1982; 10:160-165
12. Flygerring J, Hansen J, Holst B, et al: Treatment of alcohol withdrawal symptoms in hospitalized patients. *Acta Psychiatr Scand* 1984; 69:398-408
13. Pinel JPJ: Alcohol withdrawal seizures: implications of kindling pharmacology. *Biochemistry and Behavior (Suppl)* 1980; 13: 225-231
14. Butler D, Messiha F: Alcohol withdrawal and carbamazepine. *Alcohol* 1986; 3:113-129
15. Folstein MF, Folstein SE, McHugh PR: "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189-198
16. Shaw JM, Kolesar GS, Sellers EM, et al: Development of optimal treatment tactics for alcohol withdrawal. I: assessment and effectiveness of support care. *J Clin Psychopharmacol* 1981; 1: 382-387
17. Lance JW, Schwab RS, Peterson EA: Action tremor and the cogwheel phenomenon in Parkinson's disease. *Brain* 1963; 86: 95-110
18. Derogatis LR: SCL-90-R: Administration, Scoring, and Procedures Manual, I. Baltimore, Johns Hopkins University, Clinical Psychometrics Research Unit, 1977
19. Beck AT, Ward CH, Mendelson M, et al: An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4:561-571
20. Spielberger CD, Gorsuch RL, Lushene RD: STAI Manual. Palo Alto, Calif, Consulting Psychologists Press, 1970
21. Wechsler D, Stone C: Wechsler Memory Scale. New York, The Psychological Corp, 1945
22. Joffe RT, Post RM, Roy-Byrne PP, et al: Hematological effects of carbamazepine in patients with affective illness. *Am J Psychiatry* 1985; 142:1196-1199
23. Pisciotto AV: Carbamazepine: hematological toxicity, in *Anti-Epileptic Drugs*. Edited by Perry JK, Pippenger CE. New York, Raven Press, 1983
24. Brown ME, Anton RF, Malcolm R, et al: Alcoholic detoxification and withdrawal seizures: clinical support for a kindling hypothesis. *Biol Psychiatry* 1988; 24:507-514

Recent Life Events and Panic Disorder

Carlo Faravelli, M.D., and Stefano Pallanti, M.D.

The authors assessed life events during the 12 months before the onset of panic disorder in 64 patients. Compared with a control group of 78 healthy subjects, patients with panic disorder had higher scores however life events were assessed, i.e., number of events, weighted normative scores, contextual scores, and number of subjects with major events. Independent life events (those beyond the subject's control) were also more numerous and more severe among the patients. The larger number of events experienced by the patients was due to the more frequent occurrence of life stress in the month before the onset of panic disorder. Loss events had the strongest relationship to panic disorder.

(Am J Psychiatry 1989; 146:622-626)

With the abolition of the term "neurosis" and the consequent reclassification of anxiety states, the recurrent crises of acute anxiety (panic attacks), whether associated with agoraphobia or not, have acquired a new nosological autonomy (DSM-III and DSM-III-R). Panic disorder has therefore received wide attention, and many of its features have been adequately described. However, the pathogenic role of psychosocial stressors needs further clarification. Although most of the clinical descriptions of this syndrome report that the initial symptoms are often triggered by stressful life events, to our knowledge only two papers have investigated this topic on empirical grounds, focusing on the specific diagnosis of panic disorder and using a control group of normal subjects.

In a preliminary report we observed that panic patients experience more life events in the year before the onset of the illness than do healthy control subjects and that the highest concentration of life stress occurs in the last few months before the initial symptoms (1). However, no particular type of event specifically related to panic disorder was found. Roy-Byrne et al. (2) confirmed that panic patients experience more life

events, but their results differ from ours in several aspects. The most evident difference is represented by nonsignificantly different scores for the patients and control subjects in their study on the normative measures of life change used, i.e., the Holmes and Rahe (3) and Tennant and Andrews (4) scales (on the latter scale the difference was close to significant). An earlier study (5), which used nonoperational diagnostic criteria, not only noted that patients with "anxiety" had a greater degree of life events but also identified danger events as being specific causal agents for such states.

Although the three aforementioned studies are consistent in reporting the relevance of recent life events as risk factors for panic disorder, this issue deserves further consideration. Several questions, in fact, remain unanswered.

1. Is there a real increase in life stress before the onset of panic disorder and, if so, to what extent?
2. For how long do life events exert their influence as risk factors?
3. Is the number of events or their severity relevant? In other words, is there an additive factor, by which several repeated minor events may induce a pathological reaction, or, rather, an all-or-nothing effect, with a minimum severity threshold?
4. Is the excess of life stress causally linked to panic disorder, or could panic disorder be the result of particular prepathological states (e.g., latent subclinical symptoms or stress-prone personality)?
5. Is there a specific kind of life event or, rather, a particular meaning attached to specific events, by which certain experiences are more likely than others to induce panic disorder?

The present paper attempts to focus on such issues and presents the final results of a preliminary study reported previously (1).

METHOD

Subjects

During the period Jan. 1, 1984, to Dec. 31, 1985, 64 patients referred to three psychiatric outpatient facilities met the following intake criteria for the study: a DSM-III diagnosis of either panic disorder or agoraphobia with panic attacks, and onset of the illness precisely datable to within 4 months of the interview. The second criterion was necessary to ensure the reliability

Received June 1, 1988; revision received Nov. 8, 1988; accepted Nov. 23, 1988. From the Institute of Nervous and Mental Disease and Florence University Medical School, Florence, Italy. Address reprint requests to Dr. Faravelli, Istituto Malattie Nervose e Mentali, Policlinico Careggi, V. le Morgagni 85, Florence, Italy.

Supported by Italian National Research Council grant 85.0561.56.

Copyright © 1989 American Psychiatric Association.

of the retrospective investigation of life events, since it has repeatedly been reported that time may influence the recall of events (6–10).

Retrospectively, all the patients met the *DSM-III-R* criteria for panic disorder. Because the level of agoraphobia was systematically recorded on a 5-point rating scale, it was also possible to subdivide the patients into the four categories of *DSM-III-R*: seven had no evidence of phobic avoidance, 23 had mild avoidance, 20 had moderate agoraphobia, and 14 had severe agoraphobia. Seventeen patients were men and 47 were women; their mean \pm SD age was 32.29 ± 9.90 years, the mean \pm SD length of education was 10.73 ± 3.17 years, and the mean \pm SD social class level (rated 1 to 5) was 3.18 ± 0.90 . Patients were also given a semistructured interview in order to evaluate axis II diagnoses and childhood psychopathology.

The control group was drawn from a pool of 134 hospital employees and their relatives and acquaintances who volunteered to participate in the study. The original control group was selected to correspond to the 1981 census data for age, sex, marital status, social class, and education. Since the patient group was younger, it was necessary to randomly select 78 subjects from the control group in order to match the patient sample for the same variables. There were 23 men and 55 women in the control group; their mean \pm SD age was 34.84 ± 10.41 years, the mean \pm SD length of education was 11.78 ± 5.85 years, and the mean \pm SD social class level was 3.04 ± 0.88 years.

Procedure

The procedure for collecting and assessing the events has been described in detail elsewhere (11). Briefly, patients and control subjects were given a semistructured interview, derived from that of Brown and Harris (12), which extensively and systematically explored the events of the year before the onset of the illness (the year before the interview in the case of control subjects), as well as the circumstances and the context in which they occurred. Although interviewers were aware of the patient or control status of the subjects, the reports, recorded in detail, were submitted (with patients and control subjects randomly mixed) to two different pairs of assessors who were not involved in the interviews and were blind as to whether a given account referred to a patient or to a control subject. Thus, any element by which the assessors could identify whether the subjects were patients or control subjects was omitted.

The assessors had to decide the following:

1. Whether a given occurrence, as elicited by the interview, would fit any of the items on the list by Paykel et al. (13). This list is made up of 61 events, ranked in descending order of severity. A weighted score, obtained through a calibration study, is connected with each event. The most severe event ("death of child") has a score of 19.33; the 20th event, which we considered the cutoff point to distinguish severe

from nonsevere events, is "loss of personally valuable object" and has a score of 14.07; and the last (61st) event ("child married with respondent's approval") has a score of 2.94.

2. The exact time in which the event occurred. Events of more than 3 months' duration were considered long-lasting.

3. Whether the event could be dependent, i.e., under the control of the subject (in other words, whether the behavior of the subject could have determined the occurrence of the event). For instance, an event such as "sudden stroke of father" was considered unlikely to be determined by the subject and was thus assessed as independent. On the other hand, events such as "marital separation" and "loss of job because of absenteeism" were considered dependent, since they were possibly secondary to disordered behavior on the part of the subject.

4. The contextual rating, which measured separately the amount of loss, threat, and adjustment attached to each event. Loss was defined as the amount of personal (material or psychic) irreversible loss or diminution connected with the event, threat was defined as the degree of danger, uncertainty, or risk (psychic or material) that the event bore for the future of the subject, and adjustment was defined as the amount of life change necessary to cope with the modifications consequent to the event. For the purpose of such assessments, 5-point (0 to 4) rating scales were specially devised, with precisely defined anchor points. For example, one rating of loss in the area of health was as follows: score of 4=sudden death of a relative (child, parent, or spouse); score of 3=severe illness, not fully reversible (e.g., paralysis), of either the subject or a close relative; score of 2=severe but fully reversible injury (e.g., fractured leg); and score of 1=mild and fully reversible illness but one requiring a minor adjustment (e.g., subject had to give up a desired vacation because of the flu). The reliability (kappa) of this rating procedure was 0.71 for loss, 0.67 for threat, and 0.70 for adjustment.

A subject was considered to have experienced a severe event when any of the top 20 events on Paykel's list had occurred. On the basis of this procedure it was possible to obtain for each subject several normative measures of stress (number of events, weighted scores for all events and for independent events, mean score for single most severe event, and number of subjects with at least one severe event) and three contextual measures.

RESULTS

The comparisons between panic patients and control subjects are summarized in table 1. The patients experienced a significantly greater amount of life stress in every way it was measured. Forty-one patients (64.1%) had had at least one severe event, compared with 27 control subjects (34.6%); the difference was significant ($\chi^2 = 12.21$, $df = 1$, $p < 0.001$). Forty patients (62.5%) and 25 control subjects (32%) had at least

TABLE 1. Life Events of Patients With Panic Disorder and Control Subjects During the Year Before the Onset of Panic Disorder

Item	Panic Disorder Patients (N=64)		Control Subjects (N=78)		t*
	Mean	SD	Mean	SD	
Normative assessment (Paykel scale)					
Events	2.57	1.58	1.58	1.38	3.96 ^b
Total score (all events)	31.00	18.01	18.36	18.03	4.16 ^b
Chronic events score	5.86	10.08	2.69	7.12	2.19 ^c
Single highest event score	13.39	5.58	10.05	6.19	3.34 ^b
Independent events score	17.46	14.22	10.43	12.54	3.12 ^b
Single highest independent event score	11.56	6.77	6.97	7.02	3.93 ^b
Contextual assessment					
Events	3.66	3.63	2.78	2.04	2.08 ^c
Loss score	4.18	3.37	1.90	1.84	5.12 ^b
Threat score	4.90	3.31	2.83	2.71	4.10 ^b
Adjustment score	4.93	3.60	3.40	2.68	2.88 ^d

*df=140.

^bp<0.001.^cp<0.05.^dp<0.01.

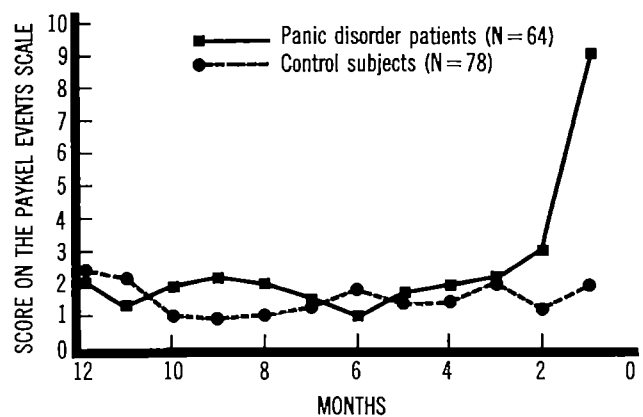
one severe independent event ($\chi^2=15.17$, $df=1$, $p<0.001$). Of the patients and control subjects, 40 (62.5%) and 22 (28.2%), respectively, had at least one loss event ($\chi^2=16.81$, $df=1$, $p<0.001$), 48 (75%) and 36 (46.1%) had at least one threat event ($\chi^2=12.11$, $df=1$, $p<0.001$), and 48 (75%) and 42 (53.8%) had at least one adjustment event ($\chi^2=6.78$, $df=1$, $p<0.01$).

The time course of events (figure 1) suggests that the greater number of events experienced by the patients was due almost entirely to the more frequent occurrence of life stress in the month before the onset of panic disorder. Such an accumulation of life events in the period immediately before the onset of the illness is also shown by the fact that of the 41 patients who experienced a severe event, 21 did so within a month of the onset of panic disorder, eight between months 1 and 2, five in the third month, two between months 4 and 6, and five between months 7 and 12 ($\chi^2=116.31$, $df=3$, $p<0.0001$). In the control group, on the other hand, the occurrence of severe events was evenly distributed throughout the whole period under study. Even when only the events judged to be independent (i.e., beyond the subject's control) were considered, the results did not vary much.

Finally, we found that the variables of age, sex, social class, education, level of agoraphobia, overall severity of illness, presence of an axis II diagnosis, and childhood psychopathology had no influence on life events.

DISCUSSION

Several methodological problems are associated with this kind of study. First, it is necessary to establish how representative the sample is. We therefore compared

FIGURE 1. Paykel Life Events Scale Scores of Patients With Panic Disorder and Control Subjects

the characteristics of our patients with those of the patients found to be affected by panic disorder in a community epidemiological survey carried out in the same catchment area (14). These patients did not differ from our sample in terms of age, sex, education, marital status, or age at onset; however, the degree of agoraphobia was higher in our patients.

While our sample is fairly representative of community cases, one must consider that the presence of a stressful event might selectively affect the probability that an individual would seek medical help. In cases in which the onset of illness has shortly followed a severe stressor, subjects could more easily consider their condition as a normal psychological reaction rather than a medical disorder and therefore be less likely to consult a physician. If this were the case, the number of life events should be less in psychiatric samples than in community cases; such a possibility would therefore emphasize the excess of life events we found. Different recruitment criteria and different treatment settings, however, could explain, at least partially, the minor differences found in the studies that investigated the relationship between life events and panic disorder. It is possible, in fact, that highly regarded institutions, which often receive patients selected on the basis of previous poor response to treatment, deal with patient groups in which the biological component of the disorder is greater. This could be one of the reasons for the differences found in the extent of the effect of life stress on panic disorder between our patients (university and private patients), those of Roy-Byrne et al. (2) (patients at the National Institute of Mental Health), and those of Finlay-Jones and Brown (5) (general practice patients). Other factors, such as the differences in the procedures of investigation and in the lifestyles of the subjects, may account for the discrepancies.

A second point concerns the reliability of the retrospective investigation of life events. It is well known that some patients may search for the causes of their illness in life events; this search for meaning (12) could lead them to attach a greater meaning to the events, thus facilitating their recall in retrospective inquiries,

compared with people for whom the events did not result in pathological states. In order to counteract these difficulties we investigated only those patients in whom the first panic attack had occurred at a short interval from the interview; used a detailed and standard interview designed to elicit explicitly almost all the possible life events; and decided not to use self-assessment ratings, which in a previous calibration study (11) proved to be less reliable.

Moreover, when we considered only those life events severe enough to warrant a high probability that they would not be ignored (the 20 most severe events on Paykel's list), a greater level of life stress among the patients was confirmed. In fact, it is unlikely that occurrences such as death or hospitalization of a close relative, severe personal disease, divorce, and loss of job would not be reported when they are explicitly mentioned.

In the light of our results, therefore, it can be said that panic patients seem to have undergone a greater amount of real life stress before the onset of panic disorder. However, as stated previously, the causal nature of the link between life events and disease deserves close attention. For other psychiatric disorders (e.g., schizophrenia) it has been shown that the greater number of life events could be the consequence of the illness rather than its cause and could result from an insidious onset or be related to particular premorbid personality features. In the case of panic disorder the onset is generally dramatic and sudden (panic attack), and the few patients for whom the onset could not be pinpointed were not taken into account. We also tried to single out those events which might be under the subject's control. Even when we considered only independent events, the markedly larger number of life events among the patients was still evident. Another factor in favor of a causative effect of the life events on panic disorder is the observation of their course over time. The sudden steep elevation in the mean life events score in the period immediately before the onset of panic disorder strongly suggests a causal link.

According to our data the difference between the panic patients and the control group was greater when the weighted scores, rather than the actual number of events, was considered. Furthermore, when we took into account, for each individual, only the single life event with the highest score, the differences remained approximately of the same magnitude. This would suggest that the crucial difference lies in the severity of the events rather than in their number; these data also seem to be compatible with the hypothesis of an all-or-nothing effect.

One last point must be considered: whether or not life events with a specific meaning might be preferentially involved in the pathogenesis of panic disorder. Finlay-Jones and Brown (5) reported that danger events were significantly overrepresented among patients with "anxiety," whereas loss events were more frequent among patients with "depression." Our data do not support this finding: Both loss and threat

events, as measured by independent assessors, had the greatest impact in determining the difference between patients with panic disorder and control subjects. The variance explained (calculated according to the point-biserial correlation [15]) was 15.8% for loss, 10.7% for threat, 5.6% for adjustment, and 3.0% for the number of events. Because these measures also had some degree of reciprocal correlation, a multiple logistic regression was carried out; it showed that loss had the heaviest loading on the logistic function. Although the present study did not have a comparison group of depressed patients, the same procedure was used in a separate investigation of life events in affective disorders (16), and the results were, to a large extent, comparable with those in the present study. The lack of agreement between our study and the study carried out in London (5) may be explained by several factors, the most important of which are the differences in diagnosis. While we selected only patients with panic disorder, Finlay-Jones and Brown (5) studied a group of subjects with "anxiety states" from among their patients who were drawn from a general practice. The description of the symptoms of the patients showed that this category was rather broad; it included acute, chronic, situational, and free-floating anxiety and consisted of only 13 patients. Research suggests that panic anxiety has several specific features that, on the one hand, distinguish it from other anxiety disorders (17–21) and, on the other hand, seem to render it close to depression (22, 23). It is not totally unexpected, therefore, that the kind of stressful events implicated in both disorders are the same.

In conclusion, our data seem to show that life events do play a role as precipitating factors in the onset of panic disorder. The degree of the association between life events and panic disorder, however, is not large. The population attributable risk (24), which indicates the proportion of cases that can be attributed to stressful life events (25) and is computed with 2 by 2 tables, varies between 30% and 39%. Other factors, therefore, must be taken into account together with life events in order to clarify the pathogenesis of panic disorder.

REFERENCES

1. Faravelli C: Life events preceding the onset of panic disorder. *J Affective Disord* 1985; 9:103–105
2. Roy-Byrne PP, Geraci M, Uhde TW: Life events and the onset of panic disorder. *Am J Psychiatry* 1986; 143:1424–1427
3. Holmes TH, Rahe RH: The social readjustment rating scale. *J Psychosom Res* 1967; 11:213–218
4. Tennant C, Andrews G: The pathogenic quality of life events stress in neurotic impairment. *Arch Gen Psychiatry* 1978; 35: 859–863
5. Finlay-Jones R, Brown GW: Types of stressful events and the onset of anxiety and depressive disorders. *Psychol Med* 1981; 11:803–815
6. Brown GW, Sklair F, Harris TO, et al: Life events and psychiatric disorder, I: some methodological issues. *Psychol Med* 1973; 3:74–87
7. Gerst MS, Grant I, Yager J, et al: The reliability of the Social Readjustment Scale—moderate and long-term stability. *J Psy-*

- chosom Res 1978; 22:519-523
8. Jenkins CD, Hurst MW, Rose RM: Life changes: do people really recall? Arch Gen Psychiatry 1979; 36:379-384
9. Monroe SM: Assessment of life events: retrospective vs concurrent strategies. Arch Gen Psychiatry 1982; 39:606-610
10. Paykel ES, Hollyman JA: Life events and depression—a psychiatric view. Trends in Neuroscience 1983; 7:478-481
11. Faravelli C, Ambonetti A: Assessment of life events in depression—a comparison of three methods. Soc Psychiatry 1983; 18: 51-56
12. Brown GW, Harris T: Social Origin of Depression: A Study of Psychiatric Disorder in Women. New York, Free Press, 1978
13. Paykel ES, Prusoff BA, Uhlenhuth EH: Scaling of life events. Arch Gen Psychiatry 1971; 25:213-218
14. Faravelli C, Guerrini Degl'Innocenti B, Giardinelli L: Epidemiology of anxiety disorders in Florence. Acta Psychiatr Scand (in press)
15. Friedman H: Magnitude of experimental effect and a table for its rapid estimation. Psychol Bull 1968; 70:245-251
16. Faravelli C, Pallanti S, Frassine R, et al: Life events and depression, in *Anxious Depression: Assessment and Treatment*. Edited by Racagni G, Smeraldi E. New York, Raven Press, 1987
17. Klein DF: Delineation of two drug-responsive anxiety syndromes. Psychopharmacologia 1964; 5:397-408
18. Raskin M, Peeke HUS, Dickman W, et al: Panic and generalized anxiety disorders: developmental antecedents and precipitants. Arch Gen Psychiatry 1982; 39:687-689
19. Crowe RR, Noyes R, Pauls DL, et al: A family study of panic disorder. Arch Gen Psychiatry 1983; 40:1065-1069
20. Torgensen S: Genetic factors in anxiety disorders. Arch Gen Psychiatry 1983; 40:1085-1089
21. Anderson DJ, Noyes R Jr, Crowe RR: A comparison of panic disorder and generalized anxiety disorder. Am J Psychiatry 1984; 141:572-575
22. Leckman JS, Weissman MM, Merikangas KR, et al: Panic disorder and major depression: increased risk of major depression, alcoholism and phobic disorders in families of depressed probands. Arch Gen Psychiatry 1983; 40:1055-1060
23. Breier A, Charney DS, Heninger GR: Major depression in patients with agoraphobia and panic disorder. Arch Gen Psychiatry 1984; 41:1129-1135
24. Lilienfeld A, Lilienfeld DG: *Foundations of Epidemiology*. Oxford, Oxford University Press, 1980
25. Cooke DJ, Hole DJ: The aetiological importance of stressful life events. Br J Psychiatry 1983; 143:397-400

Lateralization of Dementia of Depression in Stroke Patients

Karen Bolla-Wilson, Ph.D., Robert G. Robinson, M.D., Sergio E. Starkstein, M.D.,
Judith Boston, M.A., and Thomas R. Price, M.D.

In a group of stroke patients with left-hemisphere lesions, those with major depression performed significantly below nondepressed patients on four of nine cognitive domains examined with a neuropsychological test battery. Among patients with right-hemisphere stroke, those with major depression did not perform below nondepressed patients on any of the nine cognitive domains. The differential effect of depression on cognitive performance between left- and right-hemisphere lesion groups could not be accounted for by demographic variables, neurological symptoms, lesion location, or lesion size. Poststroke major depression appeared to produce a decline in cognitive performance or dementia of depression that depended on the laterality of the lesion.

(Am J Psychiatry 1989; 146:627-634)

The phenomenon of pseudodementia or dementia of depression has been of great interest to psychiatrists, neuropsychologists, and neurologists in part because it represents a form of potentially reversible dementia (1-6). Although these dementias have usually been associated with depressive disorders, several investigators have found intellectual impairments associated with personality disorders, nondepressive psychotic disorders, and anxiety disorders. Caine (3) has

suggested that the diagnosis of this type of dementia be based on the following four criteria: 1) intellectual impairment with a primary psychiatric disorder, 2) features of neuropsychological abnormality resembling neuropathologically induced intellectual deficit, 3) reversibility of the intellectual disorder with treatment of the psychiatric disorder, and 4) no apparent primary neuropathological process. The symptoms of this type of dementia include lack of motivation and drive, improvement of performance with prodding, difficulty with verbal elaboration, and poor memory retrieval (1-6). These symptoms, however, have also been associated with subcortical brain injury (6). In part because of this similarity to subcortical injury, it has been suggested that dementia of depression could be secondary to dysfunction of subcortical or biogenic amine circuits (6).

Although the existence of a primary neuropathological process has been proposed as an exclusion criterion for the diagnosis of dementia of depression, we have recently shown that depression in stroke patients led to greater intellectual impairment than could be attributed to the ischemic lesion itself (7). All patients with left-hemisphere strokes and major depression had abnormal Mini-Mental State examination scores, while just over 40% of nondepressed patients with similar brain injury had abnormal scores (7). Lesion location, lesion size, and severity of depression were each independently related to Mini-Mental State examination score (7). Starkstein et al. (8) showed that when patients with and without major depression were matched for size and location of lesion, Mini-Mental State scores were significantly lower in depressed patients than in nondepressed patients. Thus, major depressive disorder after brain injury may itself produce an intellectual impairment.

It is unclear, however, because of the relatively limited number of functions examined by the Mini-Mental State examination, whether poststroke intellectual impairment is restricted to specific cognitive processes or represents a more global cognitive decline. The present study examined the relationship between the presence or absence of poststroke major depression and pattern of cognitive performance through a detailed neuropsychological examination.

Presented at the 15th annual meeting of the International Neuropsychological Society, Washington, D.C., Feb. 18-21, 1987. Received July 29, 1987; revisions received June 9 and Sept. 26, 1988; accepted Oct. 21, 1988. From the Departments of Neurology, Psychiatry, and Neuroscience, Johns Hopkins University School of Medicine, and the Department of Neurology, University of Maryland School of Medicine, Baltimore. Address reprint requests to Dr. Bolla-Wilson, Department of Neurology, Johns Hopkins University School of Medicine, Francis Scott Key Medical Center, 4940 Eastern Ave., Baltimore, MD 21224.

Supported in part by Research Scientist Development Award MH-00163 and grant MH-40355 from NIMH; grant NS-15080 from the National Institute of Neurological and Communicative Disorders and Stroke; a grant from the University of Buenos Aires to Dr. Starkstein; and a NARSAD fellowship extension award to Dr. Starkstein.

The authors thank JoEllen Heller for help with the statistical analysis.

Copyright © 1989 American Psychiatric Association.

METHOD

Subjects

Patients included in this study were selected from those participating in the stroke data bank, sponsored by the National Institute of Neurological and Communicative Disorders and Stroke, at the University of Maryland Hospital. Fifty-three consecutive patients were included; they met the following criteria: 1) CT scan or neurological evidence of either a thromboembolic infarct or intracerebral hemorrhage of the right or left hemisphere, 2) no CT scan evidence or clinical history of prior brain injury, 3) no language deficit (patients were examined by a neurologist who was blind to all neuropsychological findings and who used stroke data bank criteria, and they were determined to have no aphasia; in addition, all patients were able to correctly perform the Complex Ideational Material Subtest from the Boston Diagnostic Aphasia Battery), 4) no history of previous psychiatric illness, alcoholism, or metabolic disorder, and 5) either major post-stroke depression or no depression, according to a psychiatric evaluation.

Procedure

Neurological examination and diagnosis were done by using criteria established by the stroke data bank (9). After giving informed consent, patients were given the Zung Depression Scale (10), the Hamilton Rating Scale for Depression (11), and a modified Present State Examination (PSE) (a semistructured psychiatric interview) (12) by a trained interviewer. All of the mood scales have been shown to give reliable and valid measures of depression in stroke patients (13–15). On the basis of the symptoms elicited by the PSE, a *DSM-III* diagnosis of major depression or no depression was made. The method used for conversion from PSE symptoms to *DSM-III* criteria has been discussed in a previous publication (14) and is available on request from the second author. The Mini-Mental State examination (16) was administered to assess a limited range of cognitive functions.

Due to the length of the neuropsychological battery (1 to 1½ hours), the test battery was administered within 2 days of the rest of the evaluation. The neuropsychological test battery consisted of 34 subtests extracted from standardized neuropsychological tests and was designed to assess nine functional domains. All participants were given the entire battery. The domains and the subtests were as follows: 1) orientation (Orientation and General Information), 2) language (reciting of months forward, Repetition of Words and Phrases [17], the Boston Naming Test [18], Reading, the Cookie Theft Picture [17], Comprehension of Complex Ideational Material [17], and Verbal Fluency for a single letter and animals [19]), 3) remote memory (General Information, Famous Faces Test), 4) verbal memory (Logical Memory [immediate and delayed re-

call] [20], the Rey Auditory Verbal Learning Test, shortened 10-item version [immediate, delayed recall] [21], Recurrent Words, Digit Span [forward/backward] [22]), 5) visual memory (Visual Reproduction [immediate, delayed recall] [20]), 6) recognition memory (Recurrent Words, Logical Memory, Rey Auditory Verbal Learning Test, Visual Reproduction), 7) visuo-perception/visuoconstruction (Block Design [22], Clock Drawing, Hooper Visual Organization Test [23]), 8) executive/motor (Alternating Fingers, Luria Motor Sequences [24], Apraxia Testing and Finger Oscillation Test [25]), and 9) frontal lobe functioning (Verbal Fluency for a single letter and animals, Alternating Fingers, Luria Motor Sequences). We found that the specificity and sensitivity of this battery in revealing significant cognitive impairments for patients with CT-verified brain lesions, compared with age- and education-matched control subjects, was 80% and 86%, respectively. The test-retest reliability (Spearman correlation) of the battery (total composite score) was 0.90 ($p < 0.01$) (K. Bolla-Wilson et al., unpublished data).

CT scan readings were done by a neurologist (S.E.S.) who was blind to clinical findings. Lesion volume (expressed as percentage of total brain volume) was calculated from the ratio of the largest cross-sectional area of the lesion on any CT scan slice to the cross-sectional area of the whole brain on the slice passing through the maximal cross-sectional area of the lateral ventricles. We have previously demonstrated the reliability of this procedure and its high correlation with other methods of determining lesion volume (26).

The anterior and posterior location of each lesion was defined as the mean distance of the anterior or posterior border of the lesion from the frontal pole, expressed as a percentage of the maximum anterior-posterior distance. CT scan slices were compared to a CT scan atlas (27), and lesion location was established by following the procedure of Levine and Grek (28).

Statistical analysis was done with means, standard deviations, analysis of variance, Student's *t* tests, and Mann-Whitney *U* tests. All tests were two-tailed. Parametric analysis was done on all data except when the data showed a markedly skewed distribution. In those cases, nonparametric analysis was done (29). Frequencies were analyzed by using chi-square tests with Yates' correction for expected cell size below 5.

RESULTS

Demographic and Psychiatric Findings

Of the 53 patients included in this study, 26 had a single left-hemisphere lesion and 27 had a single right-hemisphere lesion. The background characteristics are shown in table 1. The mean \pm SD ages for the depressed and nondepressed left-hemisphere stroke patients were 57 ± 11 and 61 ± 13 years, respectively; corresponding

TABLE 1. Demographic Characteristics of Depressed and Nondepressed Patients With Left- or Right-Hemisphere Stroke

Item	Left-Hemisphere Stroke		Right-Hemisphere Stroke	
	Major Depression (N=10)	No Depression (N=16)	Major Depression (N=8)	No Depression (N=19)
Hollingshead socioeconomic class				
I-III	1	4	0	1
IV and V	9	12	8	18
Sex				
Male	5	9	3	14
Female	5	7	5	5
Race				
Black	7	10	2	15
White	3	6	6	4
Handedness				
Left	1	3	0	2
Right	9	13	8	17
Time since stroke ^a				
<60 days	6	10	5	14
>60 days	4	6	3	5

^aMedian time since stroke for the four groups=39, 22, 39, and 16 days, respectively.

figures for the right-hemisphere patients were 54 ± 16 and 62 ± 10 years, respectively. The levels of education for the depressed and nondepressed left-hemisphere stroke patients were 8 ± 4 and 10 ± 3 years; corresponding figures for the right-hemisphere group were 10 ± 1 and 8 ± 4 years. Most of the patients were black and from lower socioeconomic classes (Hollingshead class IV or V). No significant differences were found between the depressed and nondepressed groups within the left-hemisphere and right-hemisphere lesion groups for any of the background characteristics (table 1).

The mean depression scores are presented in table 2. Within the left-hemisphere group, significantly higher mean scores were obtained by the depressed group on the Zung, Hamilton, and PSE scales than by the nondepressed group. While the mean Hamilton score for the patients with major depression was only 16, our group has demonstrated in a previous report (30) that the phenomenology of poststroke major depression is virtually identical to major depression in elderly patients without brain injury. Patients with major depression had significantly lower scores on the Mini-Mental State examination. Significantly higher scores were also obtained by the right-hemisphere depressed group on the Zung, Hamilton, and PSE scales, compared to the right-hemisphere nondepressed group. However, no significant differences were found on the Mini-Mental State examination. Two patients from the left-hemisphere group and one right-hemisphere patient did not complete the Zung scale because the interview had to be prematurely terminated due to patient fatigue and the patient was subsequently discharged before the interview could be completed.

Neurological Findings

The neurological findings among the four groups were equally distributed. Approximately 85% of patients in all groups were hemiparetic, and approximately 50% had a hemisensory deficit. Visual deficits (hemianopsia and quadrantanopsia) were found in one left-hemisphere and five right-hemisphere nondepressed patients. In these patients, all testing material was presented to the nonaffected visual field.

CT Findings

Direct lesion measurements were obtained for 37 of 53 patients. The remaining 16 patients, whose CT scans did not demonstrate a lesion, had clear and persistent neurological symptoms and their lesion localization was based on clinical criteria. The CT scan findings for each group are shown in table 3. In the left-hemisphere lesion group, a comparison of the number of depressed and nondepressed patients with cortical lesions as opposed to purely subcortical strokes (head of the caudate, thalamus, and corona radiata) revealed no statistically significant differences ($\chi^2=0.31$, $df=1$, $p=0.58$). Similarly, among the patients with right-hemisphere lesions a hypothesis of increased frequency of either cortical or subcortical lesions based on the existence of major depression versus no depression was not statistically substantiated ($\chi^2=0.16$, $df=1$, $p=0.69$). There were no statistically significant intergroup differences for left-hemisphere ($\chi^2=0.27$, $df=1$, $p=0.60$) or right-hemisphere ($\chi^2=0.89$, $df=1$, $p=0.347$) lesion groups in the frequency of ischemic versus hemorrhagic lesions on the basis of the presence or absence of depression.

The anterior border measurements (expressed as mean \pm SD percent of the anterior-posterior distance) for the depressed and nondepressed left-hemisphere stroke patients were $30.4 \pm 6.0\%$ and $37.9 \pm 20.0\%$; corresponding figures for the right-hemisphere patients were $45.9 \pm 17.0\%$ and $40.5 \pm 22.0\%$. The posterior border measurements for these four patient groups were $46.4 \pm 9.0\%$, $56.9 \pm 15.0\%$, $63.2 \pm 19.0\%$, and $64.9 \pm 20.0\%$, respectively. The mean \pm SD lesion volume measurements for the four groups were $2.0 \pm 2.0\%$, $5.3 \pm 4.0\%$, $3.5 \pm 2.0\%$, and $6.8 \pm 6.0\%$.

Intergroup comparisons (Hemisphere by Depression analysis of variance [ANOVA]) also revealed no statistically significant differences in lesion volume (hemisphere: $F=0.62$, $df=1$, 33 , $p=0.44$; depression: $F=3.03$, $df=1$, 33 , $p=0.09$; interaction: $F=0.00$, $df=1$, 33 , $p=0.98$) or in the distances of the anterior border (hemisphere: $F=1.5$, $df=1$, 33 , $p=0.23$; depression: $F=0.02$, $df=1$, 33 , $p=0.89$; interaction: $F=0.77$, $df=1$, 33 , $p=0.39$) and the posterior border (hemisphere: $F=3.66$, $df=1$, 33 , $p=0.07$; depression: $F=0.87$, $df=1$, 33 , $p=0.35$; interaction: $F=0.46$, $df=1$, 33 , $p<0.50$) of the lesion from the frontal pole.

TABLE 2. Depression and Mini-Mental State Scores of Depressed and Nondepressed Patients With Left- or Right-Hemisphere Stroke

Test	Left-Hemisphere Stroke					Right-Hemisphere Stroke						
	Major Depression (N=10)		No Depression (N=16)		Significance		Major Depression (N=8)		No Depression (N=19)		Significance	
	Mean	SD	Mean	SD			Mean	SD	Mean	SD		
Zung Depression Scale	63	10	34	9	7.39 ^a	22	53	11	36	6	4.88 ^b	24
Hamilton Rating Scale for Depression	16	3	5	6	5.17 ^a	24	16	4	6	4	6.44 ^a	25
Present State Examination	26	5	4	5	10.94 ^a	24	21	5	5	3	9.81 ^a	25
Mini-Mental State	21	6	26	5	2.38 ^c	25	25	4	24	5		

^ap<0.001.^bp<0.01.^cp<0.05.

TABLE 3. CT Scan Findings for Depressed and Nondepressed Patients With Left- or Right-Hemisphere Stroke

Lesion	Left-Hemisphere Stroke				Right-Hemisphere Stroke			
	Major Depression (N=7)		No Depression (N=12)		Major Depression (N=5)		No Depression (N=13)	
	N	%	N	%	N	%	N	%
Ischemic	6	86	10	83	3	60	12	92
Hemorrhagic	1	14	2	17	2	40	1	8
Cortical	2	29	4	33	2	40	4	31
Subcortical	3	43	6	50	2	40	3	23
Cortical and subcortical	2	29	2	17	1	20	6	46
Frontoinsular	2	29	4	33	0	0	4	31
Temporoparietal	1	14	5	42	3	60	8	62
Occipital	0	0	2	17	3	60	3	23
Thalamus	1	14	3	25	1	20	2	15
Basal ganglia/corona radiata	4	57	5	42	2	40	5	38

Neuropsychological Findings

In order to determine the specific cognitive functions that were differentially affected by depression, we clustered subtests into nine functional domain scores, as described in the Method section. This reduced the number of comparisons from 34 individual subtest scores to nine domain scores and therefore reduced the probability of a type I error. Because of differences in maximal scores on each subtest, individual subtest scores were converted to Z scores and added in order to produce the nine overall functional domain scores and a composite (all domains) score.

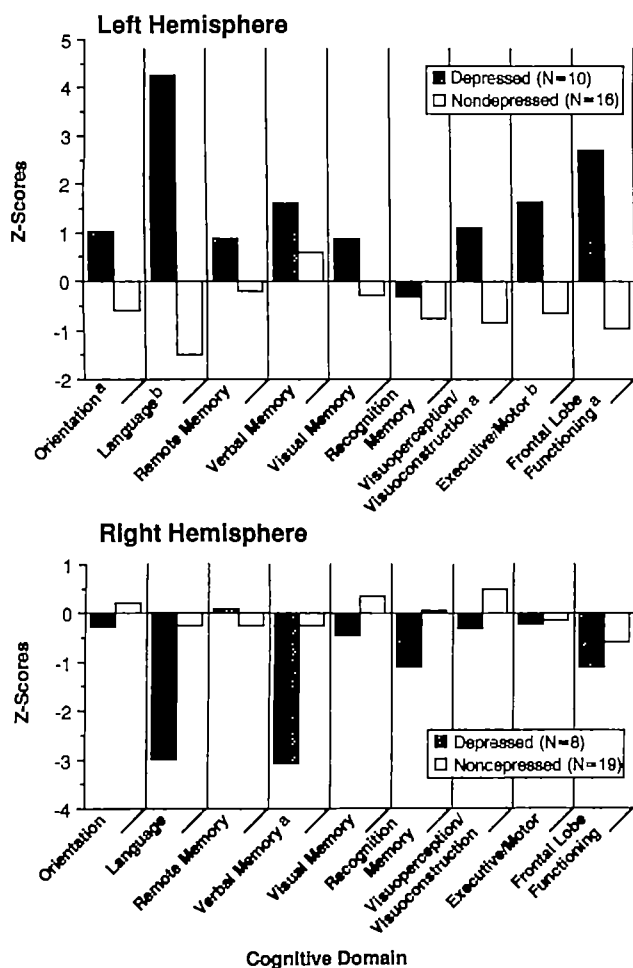
Results are illustrated in figure 1. A Hemisphere (left versus right) by Depression (depression versus no depression) ANOVA on the composite score revealed no effect for hemisphere ($F=3.41$, $df=1, 42$, $p=0.07$) or depression ($F=1.73$, $df=1, 42$, $p=0.20$), but a significant interaction ($F=6.99$, $df=1, 42$, $p<0.01$) was found. The left-hemisphere depressed group performed significantly below the left-hemisphere nondepressed group ($t=2.67$, $df=42$, $p<0.01$), the right-hemisphere depressed group ($t=2.74$, $df=42$, $p<0.01$), and the right-hemisphere nondepressed group ($t=2.25$, $df=42$, $p<0.05$). No statistically significant differences were observed between the left-hemisphere nondepressed, right-hemisphere depressed, and right-

hemisphere nondepressed groups (t values ranged from $t=-0.99$, $p=0.33$ to $t=0.37$, $p=0.71$). Within the left-hemisphere group, the presence of depression was associated with significantly lower scores in orientation ($t=2.62$, $df=22$, $p<0.02$), language ($t=2.69$, $df=22$, $p<0.01$), executive/motor ($t=2.83$, $df=24$, $p<0.01$), and frontal lobe ($t=2.73$, $df=24$, $p<0.01$) domains. The differences in the visuoconstructional/visuospatial domain scores approached significance ($t=1.87$, $df=23$, $p<0.07$). In the right-hemisphere group, there were no significant differences between the depressed and nondepressed groups on any of the nine cognitive domain scores.

Although the frequency of group compositions with respect to sex, race, and time since stroke were not significantly different, failure to find an effect of major depression on cognitive function in the right-hemisphere lesion group could be due to an imbalance between the depressed and nondepressed groups on these variables. In the right-hemisphere group, the composite scores on the battery for men versus women, blacks versus whites, and time since stroke (60 days or fewer versus more than 60 days) were compared. No significant differences were found for sex ($t=0.92$, $df=25$, $p=0.36$), race ($t=1.54$, $df=25$, $p<0.14$), or time since stroke ($t=0.42$, $df=25$, $p=0.68$).

The poorer performance shown by the left-hemi-

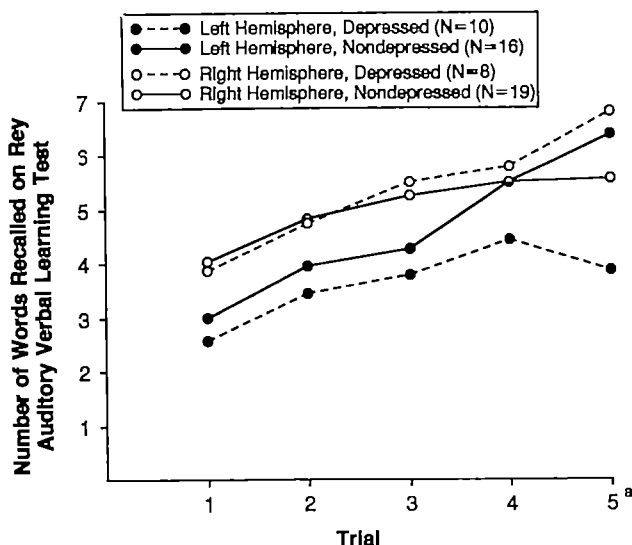
FIGURE 1. Performance on the Nine Cognitive Domains by Depressed and Nondepressed Patients With Left- or Right-Hemisphere Stroke



^a $p < 0.05$.
^b $p < 0.01$.

sphere depressed group compared to the left-hemisphere nondepressed group on the memory tests (Logical Memory, Rey Auditory Verbal Learning Test, and Visual Reproduction) could reflect failures in memory acquisition (new information into memory), memory retention (maintenance of information over an extended period of time), or memory retrieval (recall of information at a later time). When we examined the amount of "forgetting" (immediate recall errors minus delayed recall errors) on the Logical Memory test, both groups retained the same amount of information (depressed versus no depression, $\text{mean} \pm \text{SD} = 2.9 \pm 2.6$ versus 1.8 ± 1.8 ; $t = -1.27$, $df = 23$, $p = 0.22$). Therefore, depression did not appear to be associated with more retention difficulties. No significant mean error differences were found between the groups on cued recall (recognition) (depressed versus no depression, 4.6 ± 1.7 versus 3.7 ± 2.9 ; $t = 0.78$, $df = 23$, $p = 0.44$), which suggests that both groups showed similar rates of acquisition. These results suggest that with depres-

FIGURE 2. Learning Curves on the Five Trials of the Rey Auditory Verbal Learning Test for Depressed and Nondepressed Patients With Left- or Right-Hemisphere Stroke



^a $p < 0.05$.

sion, information has been acquired and retained but cannot be retrieved easily. Intact acquisition and retention with poor retrieval were also found on the Rey Auditory Verbal Learning Test and Visual Reproduction subtests. Types of errors were also analyzed. Within the left-hemisphere group, no significant group differences were found on the Rey Auditory Verbal Learning Test for the number of intrusions ($U = 77.5$, $df = 1$, $p = 0.92$) or perseverations ($U = 73.5$, $df = 1$, $p = 0.89$).

Learning curves were evaluated on the Rey Auditory Verbal Learning Test (figure 2). Both left-hemisphere and right-hemisphere depressed groups showed decay from linearity over trials, while the nondepressed groups showed the expected linear pattern of learning. The left-hemisphere depressed group showed the least amount of learning over trials and by trial 5 (a measure of overall learning) had learned significantly fewer words than the left-hemisphere nondepressed group ($t = 2.03$, $df = 30$, $p < 0.05$).

DISCUSSION

This study has demonstrated that poststroke major depression after left-hemisphere injury is associated with deficits in specific cognitive domains. In contrast, depression associated with right-hemisphere injury produced no cognitive impairment.

Before undertaking further discussion, we must address some methodological issues. While the majority of the patients ($N = 35$) were evaluated within the first 2 months after stroke, others ($N = 18$) were evaluated more than 2 months after stroke. The distribution of those evaluated 2 months after stroke, however, was not significantly different among the groups from the

distribution of those evaluated more than 2 months after stroke. When these two groups (60 days or fewer and more than 60 days) were compared by *t* test on their composite and domain scores, no significant differences were found. Another uncertainty in this study is the extent to which an atypical pattern of cerebral lateralization of cognitive functions in the six left-handed patients may have influenced our findings. While Wada tests (31) would have provided us with the extent of right-hemisphere language dominance, these tests were not performed in any of these patients. On the basis of the expected frequency of right-hemisphere dominance for language in left-handers (i.e., about 30%), only one or two of the left-handers would be expected to have reversed language laterality. We also found that none of our left-handers accounted for the minimum or maximum (outlier) values on any of the tasks, and the numbers of left-handers in the depressed and nondepressed groups were not statistically different ($\chi^2=1.93$, *df*=3, *p*=0.59). The selection of tests for inclusion in the battery tended to be biased toward tests reliant on language functions. It would have been useful to include more tasks sensitive to right- and left-anterior functions (i.e., Wisconsin Card Sorting Task, Design Fluency). The final methodological issue is that patients used in this study were predominantly a lower education group in their 50s and 60s, and the findings from this study may not be generalizable to other stroke populations.

In spite of these caveats, the most significant finding from this study was that with left-hemisphere injury, the degree of impairment was consistently worse in the group with major depression than in the nondepressed group. Although lower performance in the left-hemisphere depressed group was found in all cognitive domains, significant differences were observed in orientation, language, executive/motor, and frontal lobe domains. Thus, the combination of depression with left-hemisphere injury appeared to significantly influence cognitive functioning in specific domains. These group differences could not be explained by any of the demographic variables, neurological symptoms, or lesion volume or location.

Detailed analysis revealed that poorer memory performance in the left-hemisphere depressed group appeared to be due to difficulties in retrieval of information and not in acquisition or retention. The nonlinear pattern of learning over trials on the Rey Auditory Verbal Learning Test suggests attention/concentration difficulties and poorer sequential learning in the left-hemisphere depressed group. These findings have also been reported in patients with functional depression (6, 32, 33) and have been attributed to an inability of depressed patients to use adequate encoding strategies and organization of inputs for subsequent facilitation of recall. It has been hypothesized that the frontal lobes play a fundamental role in this process (34). Like individuals with functional depression, patients with poststroke depression did not confabulate or perseverate responses.

In the right-hemisphere group, the degree of impairment in the depressed group was not significantly different from that in the nondepressed group. The composition of the groups with respect to sex, race, and time since stroke did not account for the lack of effect of depression on intellectual function.

Could the inferior cognitive performance of the left-hemisphere depressed group, compared to the left-hemisphere nondepressed group, be due solely to lesion location? In a previous study (8), we matched major depressed and nondepressed patients for lesion size and location. Mini-Mental State scores were significantly lower among the major depressed patients than among the nondepressed patients, suggesting that depression itself interferes with cognitive functioning. While patients were not matched for lesion location in the present study, we did attempt to control for this variable by comparing depressed and nondepressed patients with lesions in the same hemisphere. In addition, detailed analysis of intrahemispheric lesion location and size revealed no significant differences between depressed and nondepressed groups with respect to cerebral structures involved, anterior/posterior extent of the lesion, or size of lesion. In fact, the left-hemisphere depressed group had the smallest mean lesion volumes of any of the groups. In this study we excluded patients with any language disorder, while in the past we excluded only patients with *severe* language disorders. This stricter selection criterion reduced the number of patients with left-anterior lesions, which may explain why we did not find a specific relationship between left-anterior lesions and either depression or dementia.

Since the frontal lobes are believed to modulate attentional processes, and more patients with left-hemisphere than right-hemisphere strokes had lesions located in the frontoinsula region, could the poor performance of the left-hemisphere depressed group be primarily attributed to an attention deficit? First, since only two depressed left-hemisphere patients had frontoinsula involvement, we do not believe frontal involvement alone could explain all the interhemispheric differences. Second, within the left-hemisphere group, approximately the same percentage of nondepressed and depressed patients had frontal involvement, and therefore the nondepressed group should have performed as poorly as the depressed group if frontal lobe involvement was responsible. Third, all groups performed equivalently on the Digits Forward and Digits Backward tasks, which are tasks of attentional ability (21). In conclusion, while some impairment of attention is commonly found in most patients with brain injury, we do not believe that patients with left-hemisphere lesions and depression showed a general decline in cognitive abilities solely because of difficulties with attention.

How can the specificity of these findings to laterality of lesion be explained? Although some investigators have suggested that depressive symptoms such as discouragement, preoccupation with depressive themes,

and poor concentration are responsible for the dementia of depression (1-6), this study found that depression after right-hemisphere or left-hemisphere lesions had different effects on cognition. This suggests that there is something about the pathophysiology of major depression after left-hemisphere injury which leads to cognitive impairment. One possible mechanism may be related to asymmetrical changes in biogenic amine concentrations. In rats, we have demonstrated that right- but not left-hemisphere injury leads to widespread depletions in norepinephrine and dopamine concentrations (35). Using positron emission tomography (PET) scanning in humans, Mayberg et al. (36) found that right- but not left-hemisphere stroke leads to increased binding of serotonin S_2 receptors in the temporal and parietal cortex. Thus the biochemical response of the brain differs depending on which hemisphere is injured. The PET scan study also found that although the left hemisphere failed to increase serotonin binding after a left-hemisphere stroke, serotonin binding in the left temporal cortex correlated with the severity of depression (36). McHugh and Folstein (6) have suggested that dementia of depression may resemble subcortical dementia because it results from subcortical as well as cortical depletions of biogenic amines. If biogenic amine depletions contribute to dementia of depression, it might occur more prominently with left-hemisphere than right-hemisphere lesions because left-hemisphere lesions produce relatively less depletion of biogenic amines and therefore fail to induce a compensatory upregulation of serotonin and receptors.

While we and other investigators have demonstrated that poststroke depression can be successfully treated with tricyclic antidepressants (37, 38), future studies are needed to determine whether intellectual function in depressed stroke patients can be improved by treatment of their depression. Thus the need to identify and treat these depressions may become even more imperative because it may lead not only to improvement in mood but also to improvement in cognitive function. Finally, future investigations that identify differences in the etiology of depression induced by left-hemisphere lesions, compared to that induced by right-hemisphere lesions, may begin to elucidate the mechanism of dementia of depression in patients without brain injury.

REFERENCES

1. Folstein MF, McHugh PR: Dementia syndrome of depression, in *Alzheimer's Disease and Related Disorders*. Edited by Katzman R, Terry RD, Bick KL. New York, Raven Press, 1978
2. Wells CE: Pseudodementia. *Am J Psychiatry* 1979; 136:895-900
3. Caine ED: Pseudo-dementia. *Arch Gen Psychiatry* 1981; 38: 1359-1364
4. Benson DF: The treatable dementias, in *Psychiatric Aspects of Neurologic Disease*, vol II. Edited by Benson DF, Blumer D. New York, Grune & Stratton, 1982
5. Caine E: The neuropsychology of depression: the pseudodementia syndrome, in *Neuropsychological Assessment of Neuropsychiatric Disorders*. Edited by Grant I, Adams K. New

- York, Oxford University Press, 1986
6. McHugh PR, Folstein MF: Psychopathology of dementia: implications for neuropathology, in *Congenital and Acquired Cognitive Disorders*. Edited by Katzman R. New York, Raven Press, 1979
7. Robinson RG, Bolla-Wilson K, Kaplan E, et al: Depression influences intellectual impairment in stroke patients. *Br J Psychiatry* 1986; 148:541-547
8. Starkstein SE, Robinson RG, Price TR: Comparison of patients with and without poststroke major depression matched for size and location of lesion. *Arch Gen Psychiatry* 1988; 45:247-252
9. Kunitz SC, Gross CR, Heyman A, et al: The pilot stroke data bank: definition, design and data. *Stroke* 1984; 15:740-746
10. Zung WWK: A self-rating depression scale. *Arch Gen Psychiatry* 1965; 12:63-70
11. Hamilton MA: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56-62
12. Wing JK, Cooper JE, Sartorius N: *Measurement and Classification of Psychiatric Symptoms: Instruction Manual for the PSE*. London, Cambridge University Press, 1974
13. Robinson RG, Starr LB, Kubos KL, et al: A two-year longitudinal study of post-stroke mood disorders: findings during the initial evaluation. *Stroke* 1983; 14:736-741
14. Robinson RG, Kubos KL, Starr LB, et al: Mood disorders in stroke patients: importance of location of lesion. *Brain* 1984; 107:81-93
15. Robinson RG, Kubos KL, Starr LB, et al: Mood changes in stroke patients: relationship to lesion location. *Compr Psychiatry* 1983; 24:555-566
16. Folstein MF, Folstein SE, McHugh PR: "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189-198
17. Goodglass H, Kaplan E: *The Assessment of Aphasia and Related Disorders*. Philadelphia, Lea & Febiger, 1976
18. Kaplan E, Goodglass H, Weintraub S: *The Boston Naming Test*. Philadelphia, Lea & Febiger, 1976
19. Benton AL, Hamsher K: *Multilingual Aphasia Examination*, rev ed. Iowa City, University of Iowa Press, 1978
20. Wechsler D: A standardized memory scale for clinical use. *J Psychol* 1945; 19:87-95
21. Lezak MD: *Neuropsychological Assessment*. New York, Oxford University Press, 1976
22. Wechsler D: *Manual for the Wechsler Adult Intelligence Scale*. New York, Psychological Corp, 1955
23. Hooper HE: *The Hooper Visual Organization Test Manual*. Los Angeles, Western Psychological Services, 1958
24. Luria AR: *Higher cortical functions in man*. New York, Basic Books, 1966
25. Reitan RM, Davison LA: *Clinical Neuropsychology: Current Status and Applications*. New York, Hemisphere Publishing Corp, 1974
26. Robinson RG, Starr LB, Lipsey JR, et al: A two year longitudinal study of post-stroke mood disorders: in-hospital prognostic factors associated with six-month outcome. *J Nerv Ment Dis* 1985; 173:221-226
27. Matsui T, Hirano A: *An Atlas of the Human Brain for Computerized Tomography*. New York, Igaku-Shoin, 1978
28. Levine DN, Grek A: The anatomic basis of delusions after right cerebral infarction. *Neurology* 1984; 34:577-582
29. Lezak MD, Gray DK: Sampling problems and nonparametric solutions in clinical neuropsychological research. *J Clin Neuropsychol* 1984; 6:101-109
30. Lipsey JR, Spencer WC, Rabins PV, et al: Phenomenological comparison of poststroke depression and functional depression. *Am J Psychiatry* 1986; 143:527-529
31. Wada J, Rasmussen T: Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. *J Neurosurg* 1960; 17:266-282
32. Cummings J, Benson D: *Dementia: A Clinical Approach*. New York, Little, Brown, 1983
33. Weingartner H, Cohen RM, Martello JDI, et al: Cognitive process in depression. *Arch Gen Psychiatry* 1981; 38:42-47
34. Eslinger PJ, Damasio AR: Severe disturbance of higher cogni-

- tion after bilateral frontal lobe ablation: patient EVR. *Neurology* 1985; 35:1731-1741
35. Robinson RG: Differential behavioral and biochemical effects of right and left hemispheric cerebral infarction in the rat. *Science* 1979; 205:707-710
 36. Mayberg HS, Robinson RG, Wong DF, et al: PET imaging of cortical S₂ serotonin receptors after stroke: lateralized changes and relationship to depression. *Am J Psychiatry* 1988; 145: 937-943
 37. Lipsey JR, Robinson RG, Pearlson GD, et al: Nortriptyline treatment of post-stroke depression: a double-blind treatment trial. *Lancet* 1984; 1:297-300
 38. Reding MJ, Orto L, Winter S, et al: Antidepressant therapy after stroke, a double blind trial. *Arch Neurol* 1986; 43:763-765

Notice of Retraction

The American Journal of Psychiatry wishes to inform its readers that the article:

Breuning SE, Davis VJ, Matson JL, and Ferguson DG: Effects of thioridazine and withdrawal dyskinesias on workshop performance of mentally retarded young adults. *Am J Psychiatry* 1982; 139:1447-1454

reported a study that an NIMH panel, after a lengthy investigation, concluded had not been carried out. We, therefore, retract our publication of that article. A similar retraction will appear in *Index Medicus*. The authors of the paper were informed by registered mail of the necessity for the publication of this retraction. Drs. Donald G. Ferguson and Johnny L. Matson concur in the retraction. Dr. Stephen E. Breuning and Ms. Vicky J. Davis do not concur in the retraction.

Perinatal Loss and Parental Bereavement

Susan K. Theut, M.D., M.P.H., Frank A. Pedersen, Ph.D., Martha J. Zaslow, Ph.D.,
Richard L. Cain, M.A., Beth A. Rabinovich, Ph.D., and John M. Morihisa, M.D.

The authors studied 25 middle-class pregnant women and their husbands who had experienced perinatal losses (16 miscarriages, seven stillbirths, and two neonatal deaths) within the previous 2 years. The Perinatal Bereavement Scale was designed to determine whether parents who have experienced a late perinatal loss (stillbirth or neonatal death) display more unresolved grief during a subsequent pregnancy and during the postnatal period than parents who have experienced a miscarriage. A three-factor repeated measures analysis of variance indicated significantly greater grief for the late-loss group, for the mothers, and during the pregnancy preceding the birth of the viable child.

(Am J Psychiatry 1989; 146:635-639)

In the present study we had four aims: 1) to empirically examine the hypothesis that there are differences between grief reactions following early and late pregnancy losses, 2) to extend knowledge about the implications of a perinatal loss for a subsequent pregnancy, 3) to examine whether grief reactions persist even after the subsequent birth of a viable child, and 4) to consider the psychological reactions of fathers to perinatal loss.

The bereavement of parents after a perinatal loss has been described in many clinical reports (1-4). The parents mourn the lost child, and the process of mourning is analogous to that experienced when an adult dies. Kirkley-Best (5), in an exploratory study of prenatal bereavement, found that losses late in pregnancy were associated with more intense grief reactions than were early losses. However, when Peppers and Knapp (6) studied maternal grief reactions to miscarriage, stillbirth, and neonatal death, they found no quantifiable difference. Methodological limitations could have contributed to this result, as the mothers in the study had experienced the perinatal losses as many as 36 years previously.

Presented at the 141st annual meeting of the American Psychiatric Association, Montreal, May 7-13, 1988. Received Aug. 10, 1988; accepted Nov. 3, 1988. From the Child and Family Research Section, Laboratory of Comparative Ethology, National Institute of Child Health and Human Development, Bethesda, Md., and the Department of Psychiatry, Georgetown University School of Medicine, Washington, D.C. Address reprint requests to Dr. Theut, Psychiatry Service 688/116A, VA Medical Center, 50 Irving St., N.W., Washington, DC 20422.

The present study was designed to provide a more rigorous examination of the hypothesis that a woman who has experienced a late perinatal loss (stillbirth or neonatal death) displays more unresolved grief during a subsequent pregnancy and postnatal period than a woman who has had a miscarriage.

The majority of women who experience a perinatal loss become pregnant within 2 years of the loss. Clinical reports (7, 8) suggest that a mother's unresolved grief can affect her emotional investment in and relationship to a subsequent baby. To our knowledge, however, no research to date has empirically examined the bereavement of parents during a subsequent pregnancy. In the study to be described, we examined the implications for the subsequent pregnancy of grief for an earlier perinatal loss.

A related question is whether the birth of a viable child diminishes the bereavement for the previous perinatal loss. Although it is plausible that a subsequent child would diminish the grief for the previous loss, research has yet to document whether such an effect occurs. In a study of the sudden, unexpected death of either spouse or a child in a motor vehicle crash, persistent long-term grieving was noted in a 4-7-year follow-up period (9). Does grieving after perinatal loss persist in a similar manner, or does it abate after a subsequent normal birth?

Finally, past research on perinatal loss has focused almost exclusively on mothers, yet Kennell et al. (1) recognized that fathers also grieve after this loss. A further purpose of the present study was to examine the father's responses to the perinatal loss during the subsequent pregnancy and postnatal period and to contrast the father's reactions with those of the mother.

METHOD

Measure Development

As part of a larger study, the Perinatal Bereavement Scale was developed to measure the bereavement of parents who have experienced a perinatal loss. Before the development of the Perinatal Bereavement Scale, a series of interviews was conducted with seven women who had experienced perinatal losses and three of their husbands. Some of the items of the scale were derived from these interviews. In addition, the preliminary

work of Kennell et al. (1) and Peppers and Knapp (6) regarding the assessment of perinatal mourning was reviewed. Some items from each of these assessments were adapted and included. Each item was intended to apply to parents who had experienced a miscarriage, stillbirth, or neonatal death.

The Perinatal Bereavement Scale consists of 26 items. (Appendix 1 is the complete questionnaire for mothers.) Responses are scored on 4-point Likert scales that range from "almost never" to "almost all the time." Items appear in both the positive and negative directions to minimize response sets. The parallel items for fathers contain wording appropriate for men. The scale requires approximately 15 minutes to complete. A summary score was obtained for each participant in our study by adding the individual item scores. The summary scores were recorded and used for the data analysis.

Sample

Announcements in local newspapers, medical centers, and childbirth classes in the Washington, D.C., metropolitan area were used to recruit 25 pregnant women and their husbands who had experienced perinatal losses. The couples were all Caucasian and highly educated. The women had a mean age of 32.0 years (range, 19.8–39.5 years). They had all graduated from high school, and their mean years of additional education was 7.0 (range, 0–8 years). The mean number of hours per week that they worked outside the home was 28 (range, 0–55 hours). The husbands' mean age was 33.0 years (range, 24.0–43.0 years). They had all graduated from high school, and their mean number of years of education beyond high school was 8.0 (range, 1.0–11.0 years). The couples had been married an average of 3.7 years (range, 1–8 years).

Each of these couples had experienced a perinatal loss within the previous 2 years. The average time between perinatal loss and the subsequent conception was 34.8 weeks. Sixteen of the couples had experienced miscarriages (before 20 weeks of gestation), seven couples had experienced stillbirths (at 20 weeks of gestation or later), and two couples had experienced neonatal deaths (within 3 days of birth). Two of the women in the miscarriage group had had elective abortions before their perinatal losses. The couples who had experienced early loss (miscarriage) and those who had experienced late loss (stillbirth or neonatal death) did not differ significantly in wife's age, years of marriage, wife's education level, or wife's employment status. After enrollment in the study, all of the women gave birth to viable children.

Procedure

During the 8th month of the pregnancy, the man and woman in each couple visited the laboratory of the Child and Family Research Section, Laboratory of Comparative Ethology, National Institute of Child

TABLE 1. Bereavement in Couples Who Experienced Birth of a Viable Child After a Perinatal Loss

Group	Score on Perinatal Bereavement Scale			
	8th Month of Subsequent Pregnancy		6 Weeks Postnatally	
	Mean	SD	Mean	SD
Mothers				
Miscarriage (N=16)	40.0	8.1	33.6	4.9
Stillbirth or neonatal death (N=9)	52.0	6.6	45.9	10.0
Fathers				
Miscarriage (N=16)	35.3	7.9	33.7	7.6
Stillbirth or neonatal death (N=9)	42.7	6.9	35.7	5.3

Health and Human Development. During this visit, they each received a description of the project and signed a consent form. Each then completed the Perinatal Bereavement Scale. The session also included additional questionnaires and interview measures not considered here. The husband and wife completed the questionnaires in separate rooms and were asked not to consult with each other. This procedure was repeated 6 weeks postnatally. The participants were assured of the confidentiality of their responses.

Data Analysis

Cronbach's alpha (10) was computed separately for the Perinatal Bereavement Scale scores of the wives and husbands at the prenatal and postnatal visits to examine the scale's internal consistency. A three-factor repeated measures analysis of variance (ANOVA) was carried out with time (prenatal and postnatal) and parent (mothers and fathers) as within-group factors and loss group (early and late loss) as the between-groups factor.

RESULTS

The alpha coefficients for the Perinatal Bereavement Scale were 0.88 (prenatal) and 0.91 (postnatal) for the mothers and 0.84 (prenatal) and 0.83 (postnatal) for the fathers, indicating acceptable internal consistency.

Table 1 presents the means and standard deviations of the scale scores for each group at each time. The ANOVA indicated that all main effects (group, time, and parent) were significant and that all interactions were not significant. The significant main effect for group ($F=14.94$, $df=1, 22$, $p<0.001$) indicated that, overall, the parents in the late-loss group grieved more than the parents in the early-loss group. The significant main effect for time ($F=41.38$, $df=1, 22$, $p<0.0001$) indicated that the parents grieved less after the

birth of the viable child than during pregnancy. The significant main effect for parent ($F=10.01$, $df=1$, 22 , $p<0.005$) indicated that the mothers grieved more than the fathers.

DISCUSSION

The results of the present study point to the usefulness of the Perinatal Bereavement Scale in assessing parental bereavement in the 8th month of the subsequent pregnancy and at 6 weeks postpartum. This study indicates that the scale has adequate internal consistency and differentiates between parents who have experienced a late perinatal loss (stillbirth or neonatal death) and those who have experienced an early loss (miscarriage). In addition, the scores on the Perinatal Bereavement Scale in this study indicated that mothers grieve more than fathers and that parents who experience either early or late loss grieve less after the birth of a viable child.

There are several plausible reasons why the parents in the late-loss group registered more bereavement than the parents in the early-loss group at both times. The fetus represents a mixture of fantasies and reality for the parents. As the pregnancy progresses and the woman experiences physical signs of the pregnancy, some of the fantasies are supported by reality. A number of investigators have empirically demonstrated the reality and intensity of parental emotional attachment to the unborn child (11–13). Klaus and Kennell (14) noted that after a woman experiences quickening, she usually begins to dream about what her baby will be like and to attribute human personality characteristics to the baby. Condon (15) noted that the first palpation of fetal movements is a significant marker in the attachment process for the mother and the father. For the parents who lose a child early in the pregnancy, the fetus is represented primarily by fantasies. For the parents who lose a child later in the pregnancy, the fetus has achieved more reality.

The parents in this study who experienced late losses had more time to form emotional and physical relationships with their babies. For the nine couples who experienced late perinatal losses, the average length of pregnancy before loss was 30 weeks. During this time, the mother would have experienced quickening and heard the fetal heart beat in the physician's office. The father would have observed changes in the mother's body as the pregnancy progressed. Thus, for both parents the baby would have assumed increasing reality. Many of the parents in our study reported selecting names, planning the nursery, and telling their family and friends about the child. The formation of the relationship continued after the stillbirth or neonatal death as each of these couples saw and held their baby, realized the sex of the child, named the child, obtained linking objects, and arranged a memorial service.

Lewis (16) observed that the birth of the subsequent child can elicit memories of the previously lost child.

Many of the parents commented that the labor and delivery, even if they occurred in another hospital and with another physician, reminded them of the previously lost child and the disappointing outcome.

The bereavement scores of the early-loss group reflected less mourning. The average time at which these parents experienced the loss was the 10th week of pregnancy. Some of them reported forming an emotional attachment to the fetus during this time. Some had already selected names and had made plans for the nursery. Many of them also stated that the pregnancy seemed unreal: the mothers had not yet experienced significant body changes signifying pregnancy, experienced quickening, or heard the fetal heart beat. Both parents reported hopes and fantasies for the baby, but there were few concrete physical details to support the emotional attachment. In contrast to the parents who experienced late losses, these parents did not see, hold, know the sex of, or experience their child in a physical form.

It appears, then, that the nature and intensity of the grieving is different when the loss occurs later in pregnancy. This difference may be related to the intensity of the physical and emotional attachment, which in turn is related to the duration of the pregnancy. In both instances there is a degree of emotional attachment to the fetus, but the physical relationship is much more intense for parents who experience late loss.

The couples in both groups in our study registered less bereavement after the birth of a viable child. Perhaps the birth of a viable child provides a corrective emotional experience that helps these parents attain a degree of grief resolution.

The significant main effect for parent revealed that the mothers grieved more than the fathers. This can be understood through examination of the psychodynamic literature on pregnancy and perinatal loss that relates to the early stages of attachment formation during pregnancy and how they differ for men and women. Furman described the uniqueness of the mother-baby relationship. She noted that the baby is a part of the mother's body during gestation and is "invested by her as a part of the self" (17, p. 214). At birth, the baby becomes more a part of the mother's mental representation. For the father, the relationship to the baby is always more one of the mental self. Thus, the mother-baby relationship is different from the father-baby relationship. The bereavement of the mother for the loss of a child is unique in that she is grieving for loss of a part of her self (17). For the father, the attachment from the beginning is different, and the resulting bereavement is thought to be different.

The results of this study agree with those from a previous exploratory study (5) but are contrary to the results reported by Peppers and Knapp (6). They examined the maternal grief of women who experienced miscarriage, stillbirth, and neonatal death. They concluded that there was no difference: the reaction to loss appeared to be as great in the case of an early miscarriage or stillbirth as it was in the case of a neonate's

death. However, Peppers and Knapp used research participants who had experienced loss as many as 36 years previously. By comparison, the present study compared reactions within 2 years. Perhaps bereavement for early loss and bereavement for late loss become indistinguishable over time. Perhaps this is what Peppers and Knapp ultimately determined.

The results of the present study suggest several directions for further research and clinical work. First, would families in a lower socioeconomic class display similar changes in bereavement between the 8th month of the subsequent pregnancy and 6 weeks postpartum? Does bereavement resolution take longer when there is less buffering from psychological stressors? What is the nature of a couple's attachment to the fetus during a subsequent pregnancy? Is this different according to whether the previous loss was early or late? How does grieving for the lost child interfere with attachment to the subsequent child? Do parents with late losses manifest less than optimal attachment to their subsequent children? After a period of time, do couples who experience early and late losses show similar degrees of bereavement? Does the mother's bereavement still exceed the father's? Finally, research is needed to determine the most appropriate way to address parental bereavement during a pregnancy that occurs after a perinatal loss.

REFERENCES

- Kennell JH, Slyter H, Klaus MH: The mourning response of parents to the death of a newborn infant. *N Engl J Med* 1970; 283:344-349
- Leon IG: Psychodynamics of perinatal loss. *Psychiatry* 1986; 49:312-324
- Lewis E: Mourning by the family after a stillbirth or neonatal death. *Arch Dis Child* 1979; 54:303-306
- Stack JM: Spontaneous abortion and grieving. *Am Fam Physician* 1980; 21:99-102
- Kirkley-Best E: Grief in response to prenatal loss: an argument for the earliest maternal attachment. *Dissertation Abstracts International* 42(B):2560, 1981
- Peppers LG, Knapp RJ: Maternal reactions to involuntary fetal/infant death. *Psychiatry* 1980; 43:155-159
- Lewis E, Page A: Failure to mourn a stillbirth: an overlooked catastrophe. *Br J Med Psychol* 1978; 51:237-241
- Bourne S, Lewis E: Delayed psychological effects of perinatal deaths: the next pregnancy and the next generation. *Br Med J* 1984; 289:147-148
- Lehman DR, Wortman CB, Williams AF: Long-term effects of losing a spouse or child in a motor vehicle crash. *J Pers Soc Psychol* 1987; 52(1):218-231
- Cronbach LJ: Coefficient alpha and the internal structure of tests. *Psychometrika* 1951; 16:297-342
- Leifer M: Psychological changes accompanying pregnancy and motherhood. *Genet Psychol Monogr* 1977; 95:55-96
- Cranley MS: Development of a tool for the measurement of maternal attachment during pregnancy. *Nurs Res* 1981; 30: 281-284
- Weaver RH, Cranley MS: An exploration of paternal-fetal attachment behavior. *Nurs Res* 1982; 32:68-72
- Klaus MH, Kennell TH: *Parent-Infant Bonding*. St Louis, CV Mosby, 1982
- Condon JT: The parental-foetal relationship—a comparison of male and female expectant parents. *J Psychosomatic Obstetrics and Gynecology* 1985; 4:271-284
- Lewis E: Stillbirth: psychological consequences and strategies of management, in *Advances in Perinatal Medicine*, vol 3. Edited by Milunsky A, Friedman E. London, Plenum, 1983
- Furman EP: Death of a newborn: care of the parents. *Birth and the Family J* 1978; 5:214-218

APPENDIX 1. Perinatal Bereavement Scale for Mothers

Directions

The statements below have been made by mothers who have experienced a pregnancy loss. Read every statement and decide which response best describes your present feelings. Then circle the appropriate letter next to each statement.

	(4) Almost All the Time	(3) Fre- quent- ly	(2) Occa- sion- ally	(1) Almost Never
1. I daydream about my lost child.	A	B	C	D
2. I worry that a pregnancy loss can happen to me again.	A	B	C	D
3. I have felt very much alone since my loss.	A	B	C	D
4. I have periods of tearfulness as I think about my lost baby.	A	B	C	D
5. I feel a need to talk to others regarding my lost child.	A	B	C	D
6. I am now able to focus on moving ahead with my life.	A	B	C	D
7. I worry that I failed to take enough precautions during the previous pregnancy, i.e., with weight, diet, smoking, sex, drinking, activity, etc.	A	B	C	D
8. I wonder what my lost baby would be like now.	A	B	C	D
9. I am preoccupied about why I experienced a pregnancy loss.	A	B	C	D
10. I feel that the actions of other people contributed to my pregnancy loss.	A	B	C	D
11. I have the resources to help me cope with my loss.	A	B	C	D
12. I still feel sad about my pregnancy loss.	A	B	C	D
13. I have dreams about my lost baby.	A	B	C	D
14. I feel guilty when I think about my lost baby.	A	B	C	D
15. I am preoccupied with thoughts about my lost child.	A	B	C	D

16. I think about the child I lost when I see other children.	A	B	C	D	21. I am overwhelmed with sadness when I think about my previous child.	A	B	C	D
17. Since my pregnancy loss, I don't feel interested in keeping up with day-to-day activities (e.g., TV, newspapers, friends).	A	B	C	D	22. I feel that my life has been on hold since my pregnancy loss.	A	B	C	D
18. I feel helpless regarding the cause of my pregnancy loss.	A	B	C	D	23. I have fantasies about my lost child.	A	B	C	D
19. I feel I have come to terms with my pregnancy loss.	A	B	C	D	24. I feel partially responsible for the loss of my child.	A	B	C	D
20. I daydream about how my life would be if I now had the baby that I lost.	A	B	C	D	25. In spite of my experience of a pregnancy loss, I am now engaged in my usual activities.	A	B	C	D
					26. I find myself blaming others for the loss of my child.	A	B	C	D

Influence of Nondepressive Psychiatric Symptoms on Whether Patients Tell a Doctor About Depression

Kathleen K. Bucholz, Ph.D., and Stephen H. Dinwiddie, M.D.

The authors studied the other recent psychiatric symptoms of 218 subjects who reported having had depressive episodes within the past year to determine the influence of the nondepressive symptoms on whether the subjects discussed the depressive episodes with a doctor. Symptoms of panic and obsessive-compulsive disorders encouraged discussion of a depressive episode, but symptoms of drug abuse/dependence inhibited such discussion. The findings illustrate the bias in studying only patients who seek treatment, point to groups of persons who may need psychiatric help, and provide insight into the complex process of help seeking.

(Am J Psychiatry 1989; 146:640-644)

Epidemiologic studies of psychiatric illness have found much higher rates of illness than are reflected by utilization of mental health services (1). It is generally accepted that the type and severity of symptoms influence the decision to seek health care (2), but there have been few studies relating particular symptoms to the decision to seek help. This is especially true in studies of psychiatric help seeking, where investigators rarely have access to information about the full spectrum of the subjects' psychiatric symptoms. Identification of clinical differences between those who choose to seek help and those who do not can bridge the gap between studies of samples of treated patients

and those of samples from the general population. Furthermore, by adding to our understanding of what brings people to treatment, efforts can be directed to locating and providing services to those in the community who might benefit from treatment but have not sought it.

In the case of depression, a better understanding of factors affecting the decision to seek help would be of great practical importance. As Dew et al. (3) have pointed out, depression is a common disorder for which effective treatment exists. Untreated, it has many serious consequences, of which suicide is only one.

Several recent studies have added to our understanding of the issue of help seeking. Dew et al. (3), in a community sample of 96 women, assessed the impact of current depressive symptoms and both current and past clinical and psychosocial characteristics on the subjects' decisions to seek various kinds of professional help during depressive episodes. Although few characteristics differentiated help seekers from non-seekers, the authors found that those who sought help from specialty mental health services had longer depressive episodes, more severe feelings of guilt and worthlessness, more suicidal ideation, and less social support than those who sought help from nonpsychiatric physicians or other professionals.

Bucholz and Robins (4), using data from 218 subjects in the Epidemiologic Catchment Area project who reported a depressive episode in the past year, examined the influence of types of depressive symptoms on the decision to discuss the depressive episode with a physician. It was found that those who had recently experienced symptoms of loss of appetite and/or weight were more likely to have discussed the depressive illness.

Both of these studies reported only the effect of depressive symptoms on the decision to seek treatment for depression. The influence of other, coexisting psychiatric symptoms on the decision to seek help has not been commonly studied. This decision presumably rests at least partly on overall psychiatric distress, and the total number of symptoms, whether due to depression or to other coexisting psychiatric illness, may serve as an indication of distress. Thus, individuals with more symptoms may be more likely to seek help than those with fewer symptoms because they have

An early version of this paper was presented at the Fifth Biennial Workshop of the Psychiatric Epidemiology/Statistics Training Programs, Pittsburgh, Pa., June 17, 1986. Received Nov. 23, 1987; revisions received June 6 and Aug. 26, 1988; accepted Nov. 16, 1988. From the Department of Psychiatry, Washington University School of Medicine. Address reprint requests to Dr. Bucholz, Department of Psychiatry, Washington University School of Medicine, 4940 Audubon Ave., St. Louis, MO 63110.

Supported by the Epidemiological Catchment Area Program, St. Louis site, NIMH grant MH-33883 (Lee N. Robins, John E. Helzer), NIMH training grant MH-14677 (Dr. Dinwiddie), NIMH training grant in psychiatric epidemiology and biostatistics MH-17104 (Dr. Bucholz), and the John D. and Catherine T. MacArthur Foundation Network on Risk and Protective Factors in the Major Mental Disorders (Dr. Bucholz).

The authors thank Drs. Linda B. Cottler, Ruth L. Fischbach, John E. Helzer, Lee N. Robins, and Richard D. Bucholz for their comments on an earlier draft of the manuscript.

Copyright © 1989 American Psychiatric Association.

higher levels of distress. On the other hand, symptoms of some psychiatric disorders, when they coexist with depression, may be more influential than others in the decision to seek help for depression. For these more complex cases, it would be helpful to understand better which factors, in addition to the depressive symptoms themselves, promote or inhibit discussion of depression with a physician.

METHOD

The Epidemiologic Catchment Area program has been described in detail elsewhere (5, 6). Briefly, it is a multisite study funded by the National Institute of Mental Health (NIMH) to estimate the prevalence of major mental disorders in the community. Five sites across the United States participate in the study; data from only one of them (St. Louis) are presented here. A multistage cluster-probability sampling strategy was used to select subjects from households and institutions. All subjects were interviewed by lay examiners using the NIMH Diagnostic Interview Schedule (DIS), a structured interview that elicits detailed information about lifetime and current psychiatric symptoms (7, 8). This information is used in a computer program to produce diagnoses based on *DSM-III* criteria. A unique feature of the DIS method is the ability to distinguish symptoms that are potentially psychiatric in origin from those that are due exclusively to a physical illness or to the use of medication, drugs, or alcohol. Only those symptoms considered to be psychiatric in origin are counted toward a psychiatric diagnosis.

Subjects for the Epidemiologic Catchment Area study were interviewed in person with the DIS at intervals approximately 1 year apart. In addition, a brief telephone interview, eliciting information on use of health and mental health services and on life events, was administered approximately 6 months after the first face-to-face interview. Eighty percent of those selected for an index interview participated in the study, and 85% of these were reinterviewed 1 year later. The most recent occurrences of all reported lifetime psychiatric symptoms, of a depressive episode, and of discussion with a physician about the depressive episode were ascertained in St. Louis during the second face-to-face interview only. Thus, the present study is based on data from the second interview.

The study sample consisted of 218 respondents (out of a total of 3,004 subjects who had a second personal interview) from both household and institutional samples in St. Louis who reported having had a depressive episode or dysthymic period in the past year. Data on these 218 subjects have been reported in detail elsewhere (4) but are summarized here for the reader's convenience. The sample was largely female (67%), under 36 years of age (53%), white (74%), currently married (54%), not college educated (72%), with annual household incomes between \$7,200 and \$21,599 (41%), in good to excellent physical health (64%), and

with some health insurance coverage (89%). Thirty-five percent reported having used specialty mental health services during their lifetimes. The majority (78%) had seen a doctor in the past year for some reason. Twenty-nine percent reported having had a discussion with a doctor in the past year about their depressive episodes.

These respondents reported symptoms in at least three of eight symptom groups and a 2-week dysphoric period or, for dysthymia, 2 years of feeling depressed. Study subjects did not necessarily meet the *DIS/DSM-III* criteria for a diagnosis of depression or dysthymia. (Diagnosis of *DIS/DSM-III* depression is based on information about symptoms experienced during the episode with the most problems, information on which is collected separately from reports of lifetime symptoms. The *DIS/DSM-III* dysthymia diagnosis requires symptoms that are evaluated in other DIS diagnostic sections.) Rather, we viewed these subjects, by virtue of their substantial depressive symptoms, as having the potential for talking about their depressive episodes with a physician. Help seeking is not predicated on having a diagnosis but on a set of factors, one of which is distress. One does not need to meet diagnostic criteria to feel distress and seek help.

The availability of information on symptoms relevant to a variety of psychiatric diagnoses made it possible to define the subjects' psychiatric comorbidity in terms of both overall symptom count and total counts of symptoms of specific psychiatric disorders. The most recent occurrence of each positive symptom was noted, and, as with the depressive or dysthymic episodes and symptoms, only symptoms present in the past year were counted.

Symptoms of the following psychiatric disorders were studied as part of this research: mania, phobia, schizophrenia, alcohol and drug abuse/dependence, antisocial personality, somatization disorder, panic disorder, and obsessive-compulsive disorder. These represented the major diagnoses studied at all Epidemiologic Catchment Area sites.

The dependent variable in the analysis was discussion with a doctor during the past year about a recent depressive episode. The discussion could have been initiated by either the respondent or the doctor. All subjects who had reported any lifetime depressive or dysthymic episodes were asked whether they had ever discussed any of them with a doctor and, if so, how recently such a discussion had occurred. The definition of "doctor" was the one used consistently throughout the DIS and included all medical doctors, osteopaths, and medical or osteopathic students.

Weighted multiple linear regression was used to determine the influence of specific groups of nondepressive psychiatric symptoms on the dependent variable, discussion with a doctor about a recent depressive episode. Weights were necessary to take into account differences in respondent selection probabilities produced by the sampling strategy. Since weights affect estimates of standard error, we used the jackknife

method of estimating standard error, by means of a technique developed at Washington University (Spitznagel, unpublished manuscript, 1985), for all reported statistics. All tests of significance were two-tailed.

Although logistic regression is usually the analysis of choice with a dichotomous dependent variable, this method offers few advantages over ordinary regression when weighted data must be analyzed, as in this case (9). Moreover, other researchers have shown that linear and logistic regressions have very few practical differences (10).

Previous research had identified the following significant influences on recent discussion of a depressive episode: age, gender, marital status, using the emergency room as the usual source of health care, reporting a worsening in physical health between the first and second personal interviews, history of use of specialty mental health services, and an interaction term for gender and marital status. This model (called the "core model") has been described in detail elsewhere (4).

Of primary interest in the present study were the effects of symptoms of particular psychiatric disorders. Because counts of symptoms of each nondepressive disorder were correlated with the overall count of psychiatric symptoms, a procedure was devised to control for total current nondepressive psychiatric symptoms while including a count of symptoms from each specific diagnostic category. For each disorder, two variables were created; one was a sum of symptoms from that disorder, the other a sum of all symptoms other than those from that disorder. Both were then entered into the core model. In this manner it was possible to assess the contribution of symptoms from that particular disorder to the dependent variable of recently discussing a depressive episode. Because constraints of the statistical program prevented studying more than one diagnosis at a time, nine separate regressions (one for each diagnosis) were computed.

RESULTS

Subjects who had not recently discussed their depressive illness with a doctor had about three fewer current symptoms of other psychiatric disorders than did recent discussers. Additional analyses revealed that subjects who had not recently discussed their depressive symptoms had significantly fewer symptoms of panic and phobia disorders. Nondiscussers who were 35 years of age or younger had significantly more recent symptoms of drug abuse/dependence, and those who were male had significantly more symptoms of antisocial personality disorder.

In the first step in the multiple regression analyses, the total number of recent nondepressive psychiatric symptoms was added to the core model. This variable did not have a significant effect on whether there had been a recent discussion of depressive symptoms, although the effect was in the expected positive direc-

TABLE 1. Multiple Regression Analyses of the Effects of Other Symptoms on Whether Patients Discussed Depressive Symptoms With a Doctor

Symptoms Added to Core Model ^a	Regression Coefficient Estimate	Two-Tailed t (df=207)	p
Panic	0.057	2.62	0.01
Phobia	0.073	1.64	0.10
Obsessive-compulsive	0.242	3.23	0.001
Drug abuse/dependence	-0.120	-3.84	0.0001
Antisocial personality	-0.029	-1.69	0.09
Alcohol abuse/dependence	-0.006	-0.32	0.75
Mania	-0.006	-0.15	0.88
Schizophrenia	0.021	0.25	0.80
Somatization	-0.004	-0.27	0.79

^aCore model included total number of current depressive symptoms, age, gender, whether separated or widowed, use of the emergency room as the usual source of care, experiencing a worsening of health in the preceding year, having previously used specialty mental health services, and an interaction term composed of gender and separated or widowed status. Also, a variable reflecting all other nondepressive psychiatric symptoms, excluding the symptom group under study in that model, was included.

tion. Next, for each of the nine psychiatric disorders, we computed a multiple regression model, adding to the core model two variables—one a sum of the symptoms of a particular disorder, the other a count of the symptoms other than those from that disorder. Table 1 summarizes the results of these analyses.

Recent symptoms of panic and obsessive-compulsive disorders had a significant effect on encouraging recent discussion of a depressive episode. However, symptoms of drug abuse and dependence significantly decreased the likelihood of such a discussion. None of the other symptom groups had a significant influence on whether there had been a recent discussion of depressive symptoms, although the effect of antisocial personality symptoms was of borderline significance. The percentages of variance explained were 33%, 31%, and 32% in the models with panic, obsessive-compulsive, and drug abuse/dependence symptoms, respectively. These percentages were greater (but not significantly so) than the 28% of variance explained in the model that included an overall count of all recent nondepressive psychiatric symptoms.

DISCUSSION

Despite the vulnerability of these retrospective data to recall bias, several observations reassure us that the data were not seriously compromised. First, the recall period of 1 year was relatively short. Second, 71% of the study subjects had not talked to a doctor about their depressive episodes, suggesting that discussion did not serve as a marker for symptom recall. Third, the presence of symptoms from other diagnostic categories actually discouraged discussion of depressive symptoms. This shows that subjects who had recently discussed depressive symptoms were not systematically

more inclined to report more symptoms than those who did not discuss depressive symptoms. While these factors do not unequivocally rule out recall bias, they make it less likely that there was systematic forgetting or reporting.

The Epidemiologic Catchment Area data did not allow us to determine which symptom(s) primarily motivated a person to discuss a recent depressive episode. However, we found that symptoms of panic disorder in these subjects were an important additional influence on the decision to talk about a recent depressive episode. This is consistent with other evidence from the catchment area program that the presence of panic symptoms significantly increased the likelihood that persons with agoraphobia would seek help (11). It may be that the sudden onset and frightening nature of panic symptoms lead people to seek help, at which time they reveal other symptoms, including those of depression, that they are experiencing simultaneously.

As with symptoms of panic disorder, coexistence of obsessive-compulsive symptoms with depression is not uncommon (12). It may be that an intercurrent depression makes the patient less able to cope with obsessive-compulsive symptoms and hence more likely to seek help at the time of the depressive episode. Conversely, the occurrence of obsessive-compulsive and depressive symptoms at the same time may be more troublesome than either kind of symptoms separately and may therefore be more likely to motivate help seeking.

Perhaps the most interesting finding was the influence of recent symptoms of drug abuse/dependence on having a recent discussion about depression. Several explanations for this finding are possible. Evidence from other studies indicates a strong relationship between substance abuse (including both drugs and alcohol) and depressive symptoms (especially suicidal ideation) (Kulbok et al., unpublished paper, 1985), but, so far, little is known of the temporal order of appearance of symptoms when depression and substance abuse coexist in the general population.

In at least some cases, it seems likely that respondents "self-medicate" for depressive symptoms or respond to these symptoms in ways other than by seeking professional help. Another potential explanation is that the importance of depressive symptoms may be outweighed by the reinforcing aspects of drug use, leading individuals to accept these symptoms as a tolerable concomitant of drug use rather than to take steps to correct the situation, since such action would place them at risk of being recognized as drug abusers or being advised to abstain from drugs. Similarly, depressive symptoms might be seen by the individual as an expected result of substance abuse that does not require medical attention. This explanation, however, is unlikely, because DIS methodology would not score a depressive symptom as being of psychiatric origin if the respondent reported it as always resulting from use of medication, alcohol, or drugs.

Our finding about the influence of drug abuse/dependence on discussion of depression also suggests

that use of drugs impairs the abuser's judgment regarding the need to seek help. It would be useful to determine whether drug symptoms have an inhibiting effect on seeking help for other disorders as well.

Social and constitutional factors may also be involved in the decision to seek help. For example, personality factors that might contribute to developing drug abuse might also work against seeking help for problems such as depressive symptoms, or the subculture of drug abusers might discourage help seeking. In sum, symptoms of drug abuse may be seen as markers for a number of factors that potentially discourage medical contact.

Although it was not statistically significant, the negative effect of current antisocial personality symptoms suggests that the presence of these symptoms, like those of drug abuse, inhibits discussion of depressive symptoms. This may reflect either the individual's disinclination to discuss such feelings or the clinician's disinclination to elicit them. Further, it may be that individuals with both types of symptoms respond to their depressive symptoms in ways other than by seeking medical attention.

The negative effects on help seeking of drug abuse/dependence and antisocial personality symptoms imply that when patients present such symptoms, the clinician should probe more deeply for depressive symptoms, since these are less likely to be spontaneously mentioned.

As with other instances of selection bias, these findings have ramifications for research carried out in treatment settings only. Combinations of symptoms of certain disorders differentially affect the likelihood that a patient will discuss a depressive episode with a physician. This study suggests some clinical differences between individuals who do and those who do not discuss their depressive symptoms and shows that subgroups of persons with depressive episodes do not seek care. These persons may be underrepresented in treatment settings. Future research will expand on these findings in an effort to understand better the complex process of seeking help for psychiatric problems.

REFERENCES

1. Shapiro S, Skinner EA, Kessler LG, et al: Utilization of health and mental health services. *Arch Gen Psychiatry* 1984; 41:971-982
2. Mechanic D: *Medical Sociology*, 2nd ed. New York, Free Press, 1978
3. Dew MA, Dunn LO, Bromet EJ, et al: Factors affecting help-seeking during depression in a community sample. *J Affective Disord* 1988; 14:223-234
4. Bucholz KK, Robins LN: Who talks to a doctor about existing depressive illness? *J Affective Disord* 1987; 12:241-250
5. Regier DA, Myers JK, Kramer M, et al: The NIMH Epidemiologic Catchment Area program: historical context, major objectives, and study population characteristics. *Arch Gen Psychiatry* 1984; 41:934-941
6. Eaton WW, Holzer CE, Von Korff M, et al: The design of the Epidemiologic Catchment Area surveys. *Arch Gen Psychiatry* 1984; 41:942-948
7. Robins LN, Helzer JE, Orvaschel H, et al: *The Diagnostic In-*

- interview Schedule, in Epidemiologic Field Methods in Psychiatry: The NIMH Epidemiologic Catchment Area Program. Edited by Eaton WW, Kessler LG. New York, Academic Press, 1985
8. Robins LN, Helzer JE, Croughan J, et al: National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. Arch Gen Psychiatry 1981; 38:381-389
 9. Godambe VP: A unified theory of sampling from finite populations. J Royal Statistical Society, Series B 1955; 17:268-278
 10. Cleary PD, Angel R: The analysis of relationships involving dichotomous dependent variables. J Health Soc Behav 1984; 25:334-348
 11. Thompson JW, Burns BJ, Bartko J, et al: The use of ambulatory services by persons with and without phobia. Med Care 1988; 26:183-198
 12. Gittelson NL: The effect of obsessions on depressive psychosis. Br J Psychiatry 1966; 112:253-259

Deceased Members of the American Psychiatric Association

The deaths of these members were reported to APA between Dec. 8, 1988, and Feb. 2, 1989.

William F. Beuscher
Martin B. Borad
Donald T. Brown
Dante V. Capra
Ronald M. Chen
Harry Diener
Maria Z. Fuchs
Russell L. Gould
Carl E. Graner, Jr.
Richard W. Gray

Sydney H. Green
Jack Greenspan
J. Rothery Haight
Nathan Hirsch
Alexander H. Hirschfeld
Claude L. Jackson
Johng Ho Kim
Henry J. Lowenfeld
Jacob Meshken
Carl Miller

John W. Mudd
James M. Murphy
Kenneth P. Nash
George L. Perkins
P. Sandlin III
John R. Stiefel
Fred G. Swartz, Jr.
Kenneth J. Tillotson

Murder and Assault Arrests of White House Cases: Clinical and Demographic Correlates of Violence Subsequent to Civil Commitment

David Shore, M.D., C. Richard Filson, Ed.D., Wayne E. Johnson, Ph.D.,
Donald S. Rae, M.A., Peter Muehrer, Ph.D., Daniel J. Kelley, M.D.,
Ted S. Davis, Ph.D., Ivan N. Waldman, M.S., and Richard Jed Wyatt, M.D.

The authors studied arrest records and clinical data on 217 persons formerly hospitalized as "White House Cases" because they were psychotically preoccupied with prominent political figures. Prior arrest for violent crime was the variable most strongly associated with arrest for violent crime after hospital discharge. Male gender and a history of weapons possession were also correlated with future violence. For those with prior violent crime arrests, hospital incidents requiring seclusion were also associated with later violence. For those without prior arrests, subsequent violence was associated with threats, living outside Washington, and command hallucinations. For those previously arrested for nonviolent crimes, only persecutory delusions were associated with later violence.

(Am J Psychiatry 1989; 146:645-651)

Very few factors have been found useful in the prediction of violent behavior. The best predictor is probably a history of previous violence. There are also a number of demographic variables that have been associated with violent crimes such as murder, forcible rape, aggravated assault, and robbery: violent criminals are statistically more likely to be young, male, poor, urban, and nonwhite (1, 2).

The relationship between psychiatric illness and violent crime has been debated for many years and continues to be controversial. In general, studies published before 1960 reported that mental patients were less

likely than nonpatients to commit violent crimes. Several more recent studies found that discharged psychiatric patients as a group committed more crimes (3), but such findings were confounded because the offending former patients often had histories of arrest before psychiatric hospitalization (4, 5). Monahan and Steadman (5) reported that when demographic factors and history of prior arrest were taken into account, mental patients as a group were not especially dangerous. There is general agreement among psychiatrists that most violent criminals are not "mentally ill" (by DSM-III axis I standards), and most psychiatric patients do not commit violent crimes (6).

In all likelihood, certain subgroups of mental patients are more likely than others to be arrested for violent crimes. Kroll and Mackenzie (7) reported that certain subgroups of patients (for instance, young males) had higher rates of violent behavior than mental patients in general. The issue of the different potential for violence of patients in certain diagnostic categories (e.g., alcohol and/or drug abusers, manic patients, paranoid schizophrenic patients) has also been discussed (6, 8-12).

We previously described (13, 14) a group of civilly committed inpatients, known as "White House Cases," who were treated at Saint Elizabeths Hospital between January 1971 and July 1974. As noted in those articles and in earlier reports on White House Cases (15, 16), delusional visitors to the White House or other government offices (who often seek a personal audience with the President) are interviewed by the Secret Service and then sent to Saint Elizabeths Hospital as White House Cases if they are considered mentally ill and potentially dangerous to themselves or others. A person who carries an illegal weapon or makes an overt threat or actual attempt on the life of a prominent political figure is arrested and handled by the judicial system rather than being hospitalized (although some of these individuals may later have forensic admissions to Saint Elizabeths Hospital). We found (13) that most of the patients in our nonforensic (civilly committed) sample were white, male, unmarried, and diagnosed as having schizophrenia (most of-

Received June 18, 1985; revisions received Sept. 16 and Sept. 26, 1988; accepted Nov. 3, 1988. From the Division of Clinical Research, NIMH. Address reprint requests to Dr. Shore, Division of Clinical Research, NIMH, Parklawn Bldg., Room 10C-06, 5600 Fishers Lane, Rockville, MD 20857.

Supported in part by U.S. Secret Service contract 85-4759.

The authors thank the following people for their assistance: Mrs. A.A. Constantino; Drs. Barbara Warner, Ross Garris, Caren Carney, Guillermo Olivos, Eugene Stammeyer, Roger Peele, Park Elliott Dietz, John Monahan, Saleem Shah, Nina R. Schooler, and Joel Dvoskin; and Messrs. Kenneth Baker, Joseph Henneberry, Thomas Lalley, Darryle Jones, Bill Garvie, Harper Wilson, and Ken Candell.

ten, paranoid schizophrenia by *DSM-II* criteria). In a 1943 study (before the introduction of antipsychotic medications), Hoffman (15) noted that in more than 80% of the White House Cases he studied, the patients did not improve during hospitalization. Beyond this, we know of no follow-up reports of the outcome in White House Cases.

For this report, we reviewed FBI arrest records collected by the Behavioral Science Staff of the U.S. Secret Service Intelligence Division, Research and Training Section. This allowed us to determine which of the civilly committed White House Case patients discharged from Saint Elizabeths Hospital by July 1, 1974, had been arrested before and/or after their hospitalizations. The records we reviewed allowed the documentation of arrests that had occurred anywhere in the United States, except for juvenile arrests, which are routinely removed from arrest records.

Studies of dangerousness or violence have used a variety of different criterion variables. For our purposes, violent outcome was defined as an arrest for murder, aggravated assault, or other assault during follow-up. For this study, those few (three) cases in which threats or assaultive behavior occurred only while the person was committing a robbery or other theft were not considered to be arrests for violent crime. Although armed robbery is categorized by the FBI as a violent crime, we grouped robbery with the nonviolent crimes for the purpose of this analysis. Since there were only two White House Case subjects with arrests for rape during follow-up, and both of these also had an arrest for murder or assault, we omitted forcible rape from consideration in this paper.

METHOD

Between Jan. 1, 1971, and July 1, 1974, 328 patients were hospitalized in nonforensic divisions of Saint Elizabeths Hospital in Washington, D.C., for evaluation and treatment as White House Cases. The Intelligence Division of the U.S. Secret Service obtained the FBI arrest records for this sample of patients. This permitted the identification of those individuals known to have been arrested for one of our index violent crimes (murder, aggravated assault, or other assault, excluding robbery) between their hospital discharge dates and May 1, 1983, when the arrest record review began. In two instances, an individual had committed a crime that was "cleared by exceptional means" (other than arrest), as when a person committing a violent crime was killed by a police officer. These instances were categorized as arrests in this study. We were also able to determine which White House Case patients had been arrested previously for the index violent crimes or for nonviolent crimes only (including robbery).

Aggravated assault, for the purposes of this study, included attempted murder, assault with a deadly weapon, and/or aggravated battery. Other assault included assault and battery, simple assault or battery,

or other assault leading to an arrest. When multiple charges arose from a single event, this was routinely counted as one arrest for the most serious of the various charges. Violations of the "threat statute" or notations regarding arrest warrants were not counted as arrests for this study. The Secret Service also identified those White House Case patients who had at some time threatened a prominent political figure.

Arrest records revealed that six of the White House Case patients were not U.S. citizens but visitors, who may have returned to their home countries after discharge. Since we did not generally have access to international arrest records, we could not adequately assess the arrest histories of these individuals; therefore, they were not included in the study. Also excluded were seven subjects whose arrest records had been purged or expunged, one subject who had been hospitalized under an alias, and 14 subjects whose medical charts showed that they had not been discharged from the hospital on or before July 1, 1974. Medical records for four White House Case hospitalizations could not be located.

Since all but one of the subjects who were violent during follow-up were male, only the male White House Cases' hospital records were reviewed. These reviews were done by two graduate student (one psychology, one medical) raters blind to pre- and posthospitalization arrest records. Data on clinical symptoms and history were obtained for 217 male White House Cases by means of a chart review form. In addition to data categories previously reported (e.g., race, age, marital status, any threat against a prominent political figure, *DSM-II* diagnosis) (13), the rating form contained 71 items to be coded as present, absent, or no information. Eleven items referred to the patients' statements or behavior regarding the political figure, 41 items concerned the patients' symptoms or behavior during the index White House Case hospitalizations, and 19 items were past symptoms or behavior noted in the hospital charts. Also noted were years of education, duration of index hospitalization, and location of the home (coded as Washington, D.C., area, other metropolitan area, rural area, etc.).

White House Case subjects with arrests for murder or assault after hospital discharge were compared with those having arrests for nonviolent crimes or no arrests at all following their index hospitalizations. We did not include as violent-arrest cases those former patients whose only arrests were for robbery or assault during a theft or robbery, for threats, for possession of drugs or weapons, for crimes against property, or for "nuisance" crimes (e.g., disorderly conduct, trespassing, and various intoxication charges).

Item frequencies and interrater reliabilities were calculated, and items with fewer than 5% positive responses were eliminated, as were items with low interrater reliability (i.e., $\kappa \leq 0.60$). Before the final data analyses, disagreements between raters were resolved by consensus of the two raters and one of the principal investigators (C.R.F.). Correlation matrices

TABLE 1. Characteristics of 217 Male White House Case Subjects Followed Up 9–12 Years After Hospital Discharge

Item	Subjects With No Arrests After Discharge (N=115) ^a		Subjects With Arrests After Discharge			
	N	%	For Nonviolent Crimes (N=71) ^b		For Violent Crimes (N=31) ^c	
			N	%	N	%
Marital status						
Never married	54	47	37	52	17	55
Married	23	20	12	17	3	10
Separated/divorced	35	30	22	31	10	32
Widowed	3	3	0	0	1	3
Diagnosis						
Paranoid schizophrenia	78	68	53	75	21	68
Other schizophrenia	20	17	10	14	5	16
Nonschizophrenic disorder	17	15	8	11	5	16

^aMean±SD age at time of hospitalization=36.9±13.6 years.^bMean±SD age at time of hospitalization=33.6±10.5 years.^cMean±SD age at time of hospitalization=34.7±12.0 years.

TABLE 2. Arrests Prior to Hospitalization and After Discharge of 217 Male White House Case Subjects

Arrest Category After Discharge	Subjects With No Prior Arrests (N=112)		Subjects With Prior Arrests			
	N	%	For Nonviolent Crimes (N=74)		For Violent Crimes (N=31)	
			N	%	N	%
No arrest (N=115)	76	68	28	38	11	35
Arrest for nonviolent crime (N=71)	24	21	37	50	10	32
Arrest for violent crime (N=31)	12	11	9	12	10	32

including outcome (presence or absence of arrest for murder or assault), history of prior arrest for murder or assault, threats against a prominent political figure, demographic factors, and clinical items were then computed. Stepwise logistic regressions including both demographic and clinical variables were carried out for the White House Cases and for subgroups based on history of prior arrest. We also used logistic regression procedures to determine whether there were significant interactions between demographic variables such as age, race, and marital status.

We should note here that the use of multiple correlations and multivariate statistics with these data is open to criticism. A large number of independent variables were entered with a relatively small number of cases and limited outcome variance. In spite of these potential problems, we believe that the exploratory nature of this research and the lack of previous studies of this type justify our approach. In this "hypothesis-generating" stage, there are risks of false negative as well as false positive results. We wish to emphasize the preliminary nature of this report and the need for replication, but we believe our data should be reported so that they can be further examined in studies that are methodologically more rigorous.

RESULTS

Thirty-one (14%) of the 217 male White House Case subjects had a total of 38 arrests for violent

crimes during the 9–12 years following hospital discharge. The mean±SD length of time between hospital discharge and the first arrest for violent crime was 47±35 months (median=43 months). There were five arrests for murder, 12 for aggravated assault, and 21 for other assaults. One hundred fifteen subjects (53%) had no arrests after discharge, and 71 (33%) had arrests for nonviolent crimes only. Table 1 lists demographic data and chart diagnoses for these subjects grouped according to posthospitalization arrest categories.

White House Case patients who were arrested for murder or assault following hospital discharge were more likely to have been arrested for these violent crimes *before* their hospitalizations as well (see table 2). Of the subjects who had had prior arrests for violent crimes, 32% had such arrests following hospital discharge, whereas only 11% of those with no prior arrests had been arrested for violent crime after their hospitalizations. We should also note that the group with an outcome of arrest for violent crime (N=31) was fairly equally divided among those having no prior arrests (39%, N=12), those with prior arrests for nonviolent crimes including robbery (29%, N=9), and those with prior arrests for violent crimes (32%, N=10).

Table 3 shows the clinical checklist item variables used for these analyses, with interrater reliability (kappa) statistics and the number and percentage of chart review forms on which each of these items was rated as present. The correlation matrix of outcome with the demographic and clinical item variables showed significant correlations between posthospitali-

TABLE 3. Chart Review (Nondemographic) Items Included in Final Analysis of Data on 217 White House Case Subjects

Item	Interrater Reliability (kappa)	Charts With Item Rated as Present	
		N	%
Behavior toward prominent political figure			
Threats at index admission	0.77	24	11
Attempt to have prominent political figure help patient	0.65	82	38
Symptoms/behavior during hospitalization			
Incidents requiring seclusion	0.92	63	29
Depressive ideation/mood	0.70	36	17
Incoherent speech	0.78	113	52
Inappropriate affect	0.84	42	20
Blunted or flat affect	0.81	70	32
Visual hallucinations	0.81	24	11
Auditory hallucinations	0.78	67	31
Command hallucinations	0.78	19	9
Delusions of outside control	0.65	24	11
Grandiose delusions	0.66	162	75
Persecutory delusions	0.69	126	58
Referential thinking	0.80	34	16
Refusal of medication	0.76	46	21
History			
Previous psychiatric hospitalization	0.77	169	78
Family history of psychiatric illness	0.91	37	17
Weapons possession	0.74	16	7
Homicidal or assaultive attempt	0.66	29	13
Military or law enforcement experience	0.91	113	52
Location of home	0.76		

zation arrest for murder or assault and both prior arrest for violent crime and nonwhite race. These last two variables were also correlated significantly with each other ($r=0.20$, $df=216$, $p=0.003$). Threats (before or after index hospitalization) against a prominent political figure were correlated significantly with post-hospitalization arrest for violent crime ($r=0.16$, $df=216$, $p=0.02$) but were not significantly associated with history of prior arrest or with race. Since, as discussed later in this paper, some threats occurred after arrest for violent crime, the relevance of this association is unclear. The only other item that was correlated significantly with subsequent arrest for violent crime was history of weapons possession, which was rated as present on 7.8% of the charts ($r=0.22$, $df=216$, $p=0.0009$).

When logistic regression was used to search for interactions between demographic variables, the only significant interaction was between age and race, with nonwhites over age 35 more likely to have arrests for violent crimes after discharge. Of the 69 nonwhite subjects, 18 committed violent crimes during follow-up, and 12 of these subjects were over 35 years of age at discharge. Of the 148 white subjects, 13 committed violent crimes during follow-up, but only three of these subjects were over age 35 at discharge from the hospital.

TABLE 4. Variables Correlated With Later Arrest for Violent Crime of 217 Male White House Case Subjects*

Variable	r	df	p
Subjects without prior arrests (N=112)			
Coming from big city other than Washington, D.C.	0.29	111	0.002
Any threat against a prominent political figure	0.25	111	0.007
Threat against prominent political figure during index admission	0.22	111	0.02
Nonwhite race	0.21	111	0.03
Living in Washington, D.C., area	-0.19	111	0.04
Command hallucinations	0.17	111	0.07
Subjects with prior arrests for nonviolent crimes (N=74)			
Persecutory delusions	0.23	73	0.05
Visual hallucinations	0.22	73	0.06
Subjects with prior arrests for violent crimes (N=31)			
Weapons history	0.54	30	0.002
Hospital incidents requiring seclusion	0.45	30	0.01
Nonwhite race	0.35	30	0.05

*Chart review items rated as present on fewer than 5% of the charts and those with poor interrater reliability ($kappa \leq 0.60$) were excluded.

Using stepwise logistic regression for the demographic and clinical variables, we found that the best predictors of posthospitalization arrest for violent crime among these subjects were prior arrest for violent crime, threats against a prominent political figure, nonwhite race, and being from a large city outside the Washington, D.C., area. No other variables made statistically significant contributions to the prediction of outcome. The lack of association of specific clinical variables with later arrest for violent crime was not surprising, given the history of unsuccessful past attempts to find such correlations and the heterogeneity of our sample. We were concerned that the subjects with prior arrests for violent crime might be very different from those with no prior arrests, and we hypothesized that different clinical items might be associated with violent outcome in different subgroups based on history of prior arrest.

To test this hypothesis, the sample of White House Cases was subgrouped according to history of prior arrest, and these subgroups' correlation matrices revealed several additional associations with violent outcome (see table 4). For those with prior arrests for violent crimes (N=31), items such as hospital incidents requiring seclusion and a history (noted in the medical record) of weapons possession were most strongly correlated with later violence. For those without prior arrests (N=112), variables such as threats against a prominent political figure, coming from a large city outside the Washington, D.C., area, and, to a lesser degree, nonwhite race were associated with postdischarge arrest for violent crime. Also, in this group with no prior arrests, command hallucinations showed a nonsignificant trend toward association with violent outcome. Among those with prior arrests for nonviolent crimes (N=74), only persecutory delusions were

correlated significantly with violent outcome; there was a trend toward association of visual hallucinations with later violence.

Stepwise logistic regressions for the three White House Case subgroups based on history of prior arrest were carried out. For those with no prior arrests, coming from a large city other than Washington, D.C., was the first item to be entered, followed by any threat against a prominent political figure (both at $p < 0.01$). The next item entered for this subgroup was command hallucinations (positive trend at $p = 0.075$). In the subgroup with prior arrests for violent crime, history of weapons possession was the first item entered, with asking help of the prominent political figure before admission entered in the next step as a negative factor (predictive of no later violence). This latter item dropped out of the equation after entry of military history as a nonsignificant negative predictor ($0.10 > p > 0.05$). Among those with prior arrests for nonviolent crimes, only persecutory delusions entered the regression (at $p < 0.05$).

DISCUSSION

Sebastiani and Foy (16) described most White House Cases as generally harmless to the President or other prominent political figures. Hoffman (15) also reported that only three of the 53 patients in his group of White House Cases were frequently combative at Saint Elizabeths Hospital; the majority were rather passive and compliant. Despite this observation, he concluded that "because of their complete lack of insight coupled with their bizarre delusional ideas, these individuals must be considered and treated as potentially the most dangerous patients we have cared for."

Thirty-one of the 217 male White House Case patients in this 9–12-year follow-up study had one or more arrests for murder or assault after hospital discharge. As we have noted, subjects arrested for robbery, drug or weapons charges, property crimes, threats, or "nuisance" offenses were not included in these figures on arrests for violent crime. None of the former patients in our sample attempted to harm a prominent political figure during follow-up, but one did shoot and kill a U.S. Secret Service agent in 1980.

Demographic Factors

When we compared former White House Case patients arrested for murder or assault after hospital discharge with those without such arrests, the violent group contained far more men than women. Three-fourths of the original White House Case sample were male, and 31 of the 32 who committed violent crimes following discharge were male. Men have consistently been found to have higher arrest rates for violent crimes (1, 2), and Tardiff and Sweillam (8) noted a higher rate of assaultive behavior by male than by female patients before psychiatric hospitalization.

Of the 31 male patients later arrested for one or more violent crimes, 10 had been arrested for violent crimes before their White House Case admissions and another nine had had prior arrests for nonviolent crimes only (see table 2). Thus, 61% of the White House Case patients who were arrested for violent crimes following hospital discharge had had some prior arrest. Of the 112 patients with no prior arrests, 12 (11%) had arrests for violent crimes during follow-up, while 10 (32%) of the 31 with prior arrests for violent crimes had such arrests during follow-up. In this group of mainly (70%) paranoid schizophrenic men, prior arrest for a violent crime seemed to be the most useful predictor of future arrest for a violent crime, consistent with reports by Monahan (1) and Rabkin (10). We should also note that a majority (68%) of these men with prior arrests for violent crimes were *not* arrested for murder or assault during a 9–12-year period following their hospitalization as White House Cases.

While age (i.e., youth) has been associated with higher rates of arrest for violent crime in the general (1, 2) and mental patient (7) populations, such an effect was not seen in our sample (table 1). This may be due to specific characteristics of our sample of White House Cases, namely, that the age range was more restricted than that of the general population and that of the overall psychiatric patient population. In our sample the median age at first arrest for murder or assault following hospital discharge was 38 years.

As noted previously, we found a significant interaction between age and race; older nonwhite subjects were more likely to have arrests for violent crimes. Given the association between nonwhite race and both urban locale and lower socioeconomic status, it could be that older nonwhite subjects had higher arrest rates because of their long-term exposure to a poor urban environment. Other potential factors influencing this interaction might have been impairment of upward socioeconomic mobility because of chronic schizophrenia or greater likelihood of arrest of nonwhite suspects. The interaction may also have been affected by the relative lack of high-quality outpatient follow-up treatments available to poor urban blacks or by problems with compliance. Clearly, there are many factors that could have been involved, and further research would help to determine whether our finding can be replicated and, if so, what is responsible for this interaction.

It appears that some of the factors associated with violent crime in the general population—namely, male gender, nonwhite race, and prior arrest for violent crime—were associated with subsequent arrest for violent crime among this sample of White House Cases. As we have noted, race and prior arrest for violent crime were significantly correlated in our sample. When these subjects were subgrouped according to their histories of prior arrest, correlations between race and violence after hospital discharge were weakened dramatically, and race did not enter into the stepwise

logistic regressions (at $p < 0.10$) in any of the three White House Case subgroups.

Clinical Factors

We did not find any particular association between DSM-II chart diagnoses of the White House Cases and arrest for violent crime following hospital discharge. Since 70% of our sample had DSM-II chart diagnoses of paranoid schizophrenia (and an additional 16% had other schizophrenia diagnoses), it was difficult to make meaningful comparisons of the arrest rates for different diagnostic groups. Therefore, this paper cannot address the issue of the relative potential for violence of various diagnostic groups (6, 8–12, 17, 18).

Threats against prominent political figures (before or after index hospitalization) were also associated with arrest for violent crime among these White House Case subjects. Macdonald (19) reported on a group of 100 hospitalized psychiatric patients who had threatened to kill. During a 5-year follow-up period, three of these 100 patients did kill another person. Among the 48 White House Case subjects who at some time threatened a political figure, one subject committed a single murder and another committed two murders during a postdischarge period of approximately 10 years. Rofman et al. (20) and others (9) also noted the importance of threats in the prediction of violence by psychiatric patients. We should note, however, that of our 31 male subjects who were arrested for murder or assault after hospital discharge, only eight (26%) had threatened a prominent political figure *before* their follow-up arrests for violent crimes, three had made threats after their arrests for violent crimes, and one had made a threat between two follow-up arrests for violent crimes. Of the 186 subjects without follow-up arrests for murder or assault, 36 (19%) had threatened a prominent political figure at some time. For four of the subjects who made threats preceding an arrest for violent crime, more than 2 years elapsed between the threat and the arrest; for the other five, there was less than 1 year (typically, several months) between threat and arrest. Of course, this applies only to threats against a prominent political figure, since we have no information about threats by White House Case subjects against their eventual victims.

There was a nonsignificant trend associating command hallucinations during hospitalization with future violence, but this effect appeared to be relevant only for the subgroup with no prior arrests. While some researchers (18, 21) have noted violent or danger-related acts by patients unexpectedly acting on command hallucinations, one recent study (22) reported no higher short-term rate of assaultive acts by patients with command hallucinations. The authors of that study noted that most patients ignore these commands but that there may be subgroups of patients having command hallucinations who are at higher risk for violent behavior. Although the authors speculated that patients with prior violent behavior, especially in re-

sponse to command hallucinations, may be at greatest risk, our White House Case data do not support this interpretation. In our sample of patients, all of whom had a history of acting on delusions or hallucinations, command hallucinations seemed to be associated with (long-term) future arrest for violent crime only for those who had had *no* prior arrests.

Persecutory delusions were the only clinical variable significantly associated with later arrest for violent crime among our subjects with prior arrests for non-violent crimes only. Several reports (9, 23) have suggested that certain violent psychotic patients suffer paranoid delusions and believe their actions to be in self-defense. It is, of course, unclear why such an association should be present in only one subgroup of the sample of White House Cases. Such questions should serve to highlight the preliminary nature of these findings and the need for replication studies.

CONCLUSIONS

The most interesting findings of this study, in our opinion, are based on the heterogeneity of our White House Case sample. Clinical and demographic factors associated with later arrest for violent crime appear to be different for White House Case subgroups based on history of prior arrest. In the subgroup of subjects who had had prior arrests for violent crimes, the two strongest individual item correlations (Pearson r) with later arrest for violent crime were history of weapons possession and hospital incidents requiring seclusion. A similar item (assault during hospitalization), which was excluded because of insufficient interrater reliability, also showed a high positive correlation with subsequent arrest for violent crime in this subgroup. Thus, for those subjects who had had prior arrests for violent crimes, certain dangerous behaviors, rather than any particular psychiatric symptoms, were associated with subsequent violence.

Steadman (11) reported that factors related to violence in the hospital differ from those associated with violence in the community and noted no relationship between hospital and community assaultiveness. Our results from the overall sample of White House Cases support this conclusion, *except* for the subjects with prior arrests for murder or assault, for whom violent behavior in the hospital may in fact be associated with violence after hospital discharge. Also, our results for this group of White House Cases strongly support Lion's emphasis on obtaining information about possession of weapons in evaluating a patient's potential for violence (18).

Among the White House Case subjects with no prior arrests, the factor most strongly associated with future violence was having come to a government office in the capital from a large city outside the Washington, D.C., area. Violent crime in general is more common in urban locales (2). Our finding may also reflect the ability to plan and the willingness to act on delusional beliefs

and/or command hallucinations. While we have noted previously (13, 14) that virtually all persons hospitalized as White House Cases came to a government office in Washington, D.C., for psychotic reasons, for those living in the Washington area, such an action required far less behavioral competence. Those patients whose behavior was the most grossly disorganized would have been less likely to get to the White House or another government office in Washington if they had not already been nearby. This is consistent with Rada's observation that assault is more common in paranoid but outwardly compensated patients than in those who are "flagrantly psychotic" (24). The combination of capacity to act and intensity of motivation based on hallucinations or delusions may have been associated to some degree with subsequent arrest for violent crime of our subjects without arrests before hospitalization.

Our findings clearly demonstrate the problems in attempting to predict outcome in heterogeneous patient populations. The subjects described in this paper were typically paranoid schizophrenic patients (according to *DSM-II*) who acted on delusions or hallucinations in coming to a government office. There appear to be subgroups based on history of prior arrest that may be relevant in terms of future arrest for violent crime. For those with prior arrests for violent crimes, a history of weapons possession (noted in the clinical chart) and behavioral outbursts requiring seclusion were associated with later violence. For those without prior arrests for violent crimes, a history of threats or the presence of clinical symptoms such as persecutory delusions or command hallucinations might be more relevant. We again point out, however, that the first posthospitalization arrests for violent crime of these subjects did not occur, on average, until almost 4 years after their hospital discharges. There are a number of possible interpretations for this long interval between discharge and arrest; these will be discussed in a future article.

We should also emphasize that these associations of clinical symptoms and behaviors with future arrest for violent crime simply suggest a *relatively* greater risk within our particular sample. Most civilly committed inpatients with persecutory delusions, command hallucinations, and/or incidents requiring seclusion will probably not be arrested for violent crimes following discharge from the hospital. Since the prediction of violence is already infamous for its high false positive rate, we do not wish to worsen this situation by suggesting that these variables are a "shortcut" to predicting violence. Factors such as (male) gender and, especially, prior history of violence still appear to be far more useful than clinical variables in the prediction of future violence. Clearly, additional research and attempts to obtain relevant data from other patient samples are needed.

REFERENCES

1. Monahan J: The Clinical Prediction of Violent Behavior: US Department of Health and Human Services Publication ADM 81-921. Washington, DC, DHHS, 1981
2. Report to the Nation on Crime and Justice: The Data. Washington, DC, US Department of Justice, Bureau of Justice Statistics, 1983
3. Sosowsky L: Crime and violence among mental patients reconsidered in view of the new legal relationship between the state and the mentally ill. *Am J Psychiatry* 1978; 135:33-42
4. Brill H, Malzberg B: Statistical report on the arrest record of male ex-patients, age 16 and over, released by NY state mental hospitals during the period 1946-1948, in *Criminal Acts of Ex-Mental Hospital Patients* (suppl 153). Washington, DC, American Psychiatric Association Mental Hospital Service, Aug 1962
5. Monahan J, Steadman HJ: Crime and mental illness: an epidemiological approach, in *Crime and Justice: An Annual Review of Research*, vol 4. Edited by Tonry M, Morris N. Chicago, University of Chicago Press, 1983
6. Shah SA: Dangerousness and mental illness: some conceptual, prediction, and policy dilemmas, in *Dangerous Behavior: A Problem in Law and Mental Health*: US Department of Health, Education, and Welfare Publication ADM 78-563. Edited by Frederick CJ. Washington, DC, DHEW, 1978
7. Kroll J, Mackenzie TB: When psychiatrists are liable: risk management and violent patients. *Hosp Community Psychiatry* 1983; 34:29-37
8. Tardiff K, Sweillam A: Assault, suicide, and mental illness. *Arch Gen Psychiatry* 1980; 37:164-169
9. Hafner H, Boker W: Mentally disordered violent offenders. *Soc Psychiatry* 1973; 8:220-229
10. Rabkin JG: Criminal behavior of discharged mental patients: a critical appraisal of the research. *Psychol Bull* 1979; 86:1-27
11. Steadman HJ: Special problems in the prediction of violence among the mentally ill, in *Violence and the Violent Individual*. Edited by Hays JR, Roberts TK, Solway KS. New York, Spectrum, 1981
12. Binder RL, McNiel DE: Effects of diagnosis and context on dangerousness. *Am J Psychiatry* 1988; 145:728-732
13. Shore D, Filson CR, Davis TS, et al: White House cases: psychiatric patients and the Secret Service. *Am J Psychiatry* 1985; 142:308-312
14. Shore D, Filson CR, Johnson WE: Violent crime arrests and paranoid schizophrenia: the White House case studies. *Schizophrenia Bull* 1988; 14:279-281
15. Hoffman JL: Psychotic visitors to government offices in the national capital. *Am J Psychiatry* 1943; 99:571-575
16. Sebastiani JA, Foy JL: Psychotic visitors to the White House. *Am J Psychiatry* 1965; 122:679-686
17. Giovannoni JM, Gurel L: Socially disruptive behavior of ex-mental patients. *Arch Gen Psychiatry* 1967; 17:146-153
18. Lion JR: Violence in schizophrenic outpatients. *Schizophrenic Outpatient* 1984; 2:1-11
19. Macdonald JM: *Homicidal Threats*. Springfield, Ill, Charles C Thomas, 1968
20. Rofman ES, Askinazi C, Fant E: The prediction of dangerous behavior in emergency civil commitment. *Am J Psychiatry* 1980; 137:1061-1064
21. Yesavage JA: Inpatient violence and the schizophrenic patients. *Acta Psychiatr Scand* 1983; 67:353-357
22. Hellerstein D, Frosch W, Koenigsberg HW: The clinical significance of command hallucinations. *Am J Psychiatry* 1987; 144:219-221
23. Loucas K: Assessing dangerousness in psychotics, in *Dangerousness: Psychiatric Assessment and Management*. Edited by Hamilton JR, Freeman H. London, Gaskell (Royal College of Psychiatrists), 1982
24. Rada RT: The violent patient: rapid assessment and management. *Psychosomatics* 1981; 22:101-109

Growth Rate in Adolescents With Obsessive-Compulsive Disorder

Susan D. Hamburger, M.S., Susan Swedo, M.D., Agnes Whitaker, M.D.,
Mark Davies, M.P.H., and Judith L. Rapoport, M.D.

In an epidemiological study of 5,596 high school students, the authors identified 20 adolescents with obsessive-compulsive disorder and compared their physical size to that of adolescents of the same sex with no obsessive-compulsive symptoms. The obsessive-compulsive boys (N=11) were shorter and weighed less than the other boys (N=2,479) and were shorter than a subsample of normal boys (N=33) and boys with other psychiatric diagnoses (N=16). Regression analysis showed a flatter growth pattern through adolescence for the obsessive-compulsive boys (although within the 95% confidence limits for the other boys), suggesting a subtle neuroendocrine dysfunction in obsessive-compulsive disorder.

(Am J Psychiatry 1989; 146:652-655)

Obsessive-compulsive disorder in childhood is virtually identical to adult obsessive-compulsive disorder, and when it arises early in life, it is remarkably continuous from childhood to adulthood (1). The disorder is rare in clinical populations; the reported incidence is 1% in child psychiatric inpatients (2) and the reported prevalence is 0.2% in total child clinical populations (3).

Until recently, obsessive-compulsive disorder was viewed as a symptom of unconscious conflict. How-

ever, the intractability of obsessive-compulsive disorder to traditional psychotherapeutic intervention, its association with a number of neurological diseases (4, 5), and the often dramatic selective response to new medications (6, 7, 8) suggest a biological basis for the disorder.

In an ongoing study of over 70 obsessive-compulsive adolescent patients, we had the clinical impression that these patients, especially boys, were small physically and had a somewhat delayed onset of puberty. We had the opportunity to test this impression in a nonreferred population derived from a two-stage epidemiological study of adolescent psychopathology in a county-wide population of 5,596 high school students. The study provided systematic self-report data on height and weight for the entire student population (9).

We examined data on height and weight from this epidemiological survey, which included 20 nonreferred adolescents with obsessive-compulsive disorder, to determine whether obsessive-compulsive adolescents are physically smaller than their peers. Because the survey included adolescents with affective and anxiety disorders, we were able to obtain age- and sex-matched comparison subgroups of adolescents with no psychiatric illness and adolescents with psychiatric diagnoses other than obsessive-compulsive disorder.

METHOD

The sample consisted of 5,596 students, the total 9th- to 12th-grade enrollment in a semirural county that has a total population of 84,429 and is located 80 miles from New York City. All eight high schools in the county, public and private, were surveyed by questionnaires administered to all students as part of the school health curriculum; the overall completion rate was 91%. The respondents included 2,564 boys

Received May 23, 1988; revision received Oct. 20, 1988; accepted Nov. 16, 1988. From the Child Psychiatry Branch, NIMH, and the Division of Child Psychiatry, New York State Psychiatric Institute, New York. Address reprint requests to Ms. Hamburger, Child Psychiatry Branch, NIMH, Bldg. 10, Rm. 6N-240, 9000 Rockville Pike, Bethesda, MD 20892.

Supported by Biomedical Research Support Grant from the New York State Psychiatric Institute, by NIMH grants MH-40527 (to Dr. Whitaker) and MH-16434, and by NIMH Clinical Research Center grant MH-30906.

TABLE 1. Age and Body Size Measures of Adolescents With and Without Obsessive-Compulsive Disorder, Subclinical Obsessive-Compulsive Features, or Compulsive Personality Disorder From a Community-Based Sample

Adolescent Group	Age (years)		Height (in)		Weight (lb)		Body Mass Index ^a	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Obsessive-compulsive disorder								
Boys (N=11)	15.5	1.4	67.2 ^b	2.5	137.0 ^c	11.6	3.0	0.3
Girls (N=9)	16.4	1.0	64.0	3.2	121.9	12.6	2.9	0.3
Subclinical features								
Boys (N=4)	15.2	1.5	69.5	3.4	165.0	26.8	3.4	0.3
Girls (N=10)	16.4	1.2	63.1 ^d	1.0	126.5	20.5	3.2	0.5
Compulsive personality disorder								
Boys (N=5)	15.8	1.2	69.6	2.7	154.5	25.6	3.1	0.3
Girls (N=5)	17.2	0.4	65.2	1.9	130.0	20.0	3.1	0.4
All others								
Boys (N=2,479)	15.7	1.3	68.6	3.8	146.4	28.8	3.1	0.5
Girls (N=2,477)	15.6	1.2	64.2	2.8	123.4	21.5	2.9	0.5

^aWeight/height²×100.^bSignificantly shorter than the boys with no obsessive-compulsive symptoms ($t=1.95$, $df=10$, $p<0.05$).^cSignificantly lighter than the boys with no obsessive-compulsive symptoms ($t=2.56$, $df=10$, $p<0.05$).^dSignificantly shorter than the girls with no obsessive-compulsive symptoms ($t=3.42$, $df=9$, $p<0.05$).

(50.2%) and 2,544 girls (49.8%), evenly distributed (24%–26%) across grades 9 to 12. Their ages ranged from 12 to 22 years; those who were aged 13 or younger (less than 2%) and those who were older than 18 years (less than 1%) were excluded from this study. The majority of the students (94%) were white. The Hollingshead index (10) distribution for this sample was 5% from class V, 15% from class IV, 24% from class III, 37% from class II, and 20% from class I.

The survey questionnaire contained the Eating Symptoms Inventory (9), the Eating Attitudes Test (9), the Beck Depression Inventory, and the Leyton Obsessional Inventory—Child Version (9, 10), and also elicited demographic data, medical history, height, and weight. As a validity check of self-reported heights and weights in this sample, a school nurse at one of the general public high schools weighed and measured the height of over 400 students within 3 weeks of the survey administration. Correlations of 0.91 between reported and actual heights and 0.96 between reported and actual weights of these students were obtained.

Within 3–9 months after the survey, clinicians administered individual semistructured clinical interviews to a stratified sample of the same students. Strata were defined by high scores on the instruments used to assess symptoms of obsessive-compulsive, depressive, anxiety, and eating disorders. A comparison group was defined by low scores on all assessments and was included in the stage 2 interviews.

On the basis of the individual interviews of those adolescents who had high scores on the Leyton Obsessional Inventory—Child Version, diagnoses were made by the clinician/interviewer and reviewed by one other clinician. Three obsessive-compulsive spectrum diagnoses were made: 1) obsessive-compulsive disorder (*DSM-III*: past or current, $N=20$), 2) compulsive personality disorder (*DSM-III*: lifelong patterns of rigidity, stubbornness, indecisiveness, and preoccupation with details, $N=10$), and 3) subclinical obsessive-com-

pulsive features (several obsessive-compulsive symptoms with a definite date of onset, noncontinuous, clearly ego dystonic but not meeting full criteria for obsessive-compulsive disorder, $N=14$). A kappa value of 0.85 was obtained for overall agreement between clinicians on these diagnoses (11).

As 91% of the high school population of this county completed valid questionnaires, it was assumed that the students comprised the adolescent population of this county. The small group of students with any obsessive-compulsive symptoms ($N=44$) and the smaller subgroups (obsessive-compulsive disorder, compulsive personality disorder, and subclinical obsessive-compulsive features) were compared by sex to the rest of the adolescent population (excluding the 44 students with any obsessive-compulsive symptoms) with respect to several measures of body size (height, weight, and body mass index [a measure of relative body weight that correlates highly with adiposity: weight in kilograms divided by height in centimeters squared times 100]) and a crude measure of pubertal status (whether girls have begun menstruation and whether boys have axillary hair).

As hypothesized, a significant difference in height was found between the subgroup of boys with the diagnosis of obsessive-compulsive disorder and the boys with no obsessive-compulsive symptoms (table 1). Because of the difference in sample size ($N=11$ and $N=2,479$), a subsample ($N=33$) of boys with no obsessive-compulsive symptoms was then obtained by randomly selecting three boys who were the same age and attended the same school as each boy with obsessive-compulsive disorder. We also selected a subgroup of 16 age-matched boys with no obsessive-compulsive symptoms who had received a *DSM-III* diagnosis other than obsessive-compulsive disorder or an eating disorder during the stage 2 interviews; this subgroup included boys who had one or more diagnoses of adjustment disorder ($N=2$), panic disorder ($N=3$), sim-

ple or social phobia (N=6), major depressive disorder (N=2), conduct disorder (N=2), dysthymic disorder (N=3), generalized anxiety disorder (N=2), separation anxiety (N=1), or avoidant disorder (N=1).

RESULTS

The individual groups of students who received the diagnosis of obsessive-compulsive disorder, subclinical obsessive-compulsive features, or compulsive personality disorder were compared to the other students of the same sex on the variables of height, weight, body mass index, and self-report estimate of current pubertal status. One-sample *t* tests were calculated by using the group with no obsessive-compulsive symptoms as the population mean (table 1). As hypothesized, the boys with obsessive-compulsive disorder were significantly shorter and weighed less than the boys without obsessive-compulsive symptoms. In addition, the girls with subclinical obsessive-compulsive features were significantly shorter than the girls without obsessive-compulsive symptoms. No other statistical differences were found in any subgroup of either sex.

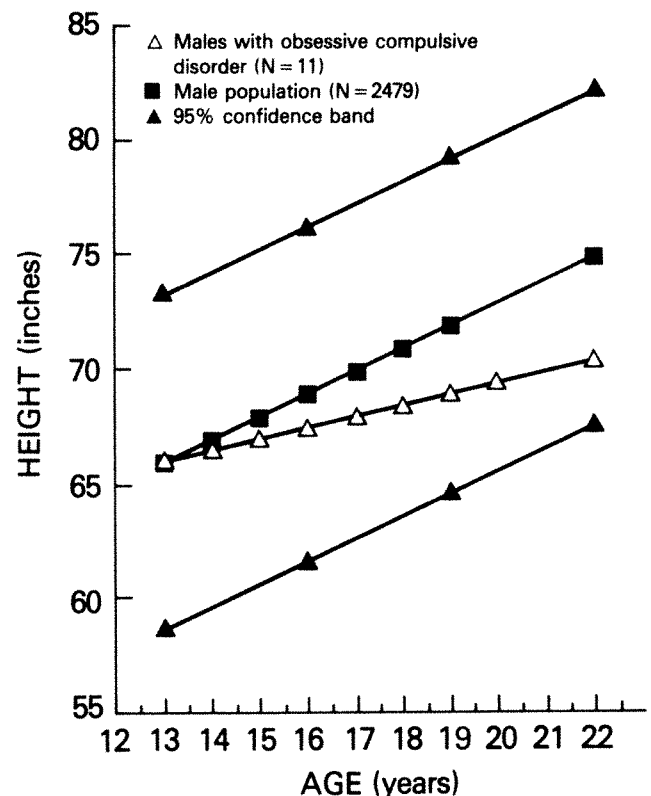
A regression analysis examining the relationship between height and age for boys without obsessive-compulsive symptoms and boys with obsessive-compulsive disorder showed that the boys without obsessive-compulsive symptoms had a steeper slope (0.98, SE=0.06) than did the obsessive-compulsive boys (0.48, SE=0.55). The difference between the slopes was not statistically significant (one-sample *t* test for differences in slopes, $p=0.38$) but suggested that obsessive-compulsive boys have a flattened growth pattern compared to boys without obsessive-compulsive symptoms (figure 1). The regression line of age and height for the obsessive-compulsive boys is within the 95% confidence limits of the regression line of age and height for the boys without obsessive-compulsive symptoms.

Age-matched subgroups of boys with no psychiatric illness (N=33) and with other psychiatric diagnoses (N=16) were compared to the boys with obsessive-compulsive disorder on the same independent variables (table 2). The results of the Wilcoxon tests (12), a nonparametric test used because the independent variables were not normally distributed, again indicated that the boys with obsessive-compulsive disorder were shorter than both comparison groups of boys without obsessive-compulsive symptoms. There were no significant differences between the boys with obsessive-compulsive disorder and the two comparison groups of boys without obsessive-compulsive symptoms with respect to weight, body mass index, and pubertal status.

DISCUSSION

We found that an epidemiologically derived, nonreferred sample of adolescent boys with obsessive-compulsive disorder were physically smaller (shorter and

FIGURE 1. Regression Lines of Age and Height for Adolescent Boys With Obsessive-Compulsive Disorder and Adolescent Boys With No Obsessive-Compulsive Symptoms From a Community-Based Sample



lighter in weight) than all other adolescent boys in their county of residence. The obsessive-compulsive boys were also shorter than age-matched subgroups of boys with no psychiatric illness and boys with psychiatric diagnoses other than obsessive-compulsive disorder from this same community-based sample, indicating some specificity for this finding. The difference in slopes of the regression lines that show the relationship between height and age suggests that boys with obsessive-compulsive disorder have a flatter growth pattern through adolescence, although the regression line was still within the 95% confidence limits of the regression line for the boys without obsessive-compulsive symptoms.

The girls with obsessive-compulsive disorder and the boys and girls with compulsive personality disorder did not differ significantly from the girls or boys with no obsessive-compulsive symptoms with respect to size or pubertal status. The girls with subclinical obsessive-compulsive features were shorter than the girls with no obsessive-compulsive symptoms but did not differ in weight, body mass index, or pubertal status. The adolescents diagnosed as having subclinical obsessive-compulsive features and the boys with compulsive personality disorder also did not differ significantly from the boys with no obsessive-compulsive symptoms and in fact tended to be taller and heavier, a finding that is

TABLE 2. Age, Body Size Measures, and Pubertal Status of Adolescent Boys With Obsessive-Compulsive Disorder and Age-Matched Subgroups of Boys With No Obsessive-Compulsive Symptoms From a Community-Based Sample

Adolescent Boys	Age (years)		Height (in)		Weight (lb)		Body Mass Index ^a		Axillary Hair (%)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Yes	No
No psychiatric illness (N=33)	15.5	1.4	69.7	3.3	145.8	32.3	3.0	0.6	88	12
Other psychiatric diagnoses (N=16)	15.6	1.2	70.3	3.6	147.1	22.2	3.0	0.4	69	31
Obsessive-compulsive disorder (N=11)	15.5	1.4	67.2 ^b	2.5	137.0	11.6	3.0	0.3	82	18

^aWeight/height³×100.^bSignificantly shorter than boys with no psychiatric illness and boys with other psychiatric diagnoses (Wilcoxon two-sample test [normal approximation]: Z=2.27, p=0.02, and Z=2.26, p=0.02, respectively).

puzzling and does not support a continuum for height within the three obsessive-compulsive subgroups. There were not many subjects in our diagnostic subgroups, but we found no evidence to suggest that adolescents with subclinical obsessive-compulsive features or boys with compulsive personality disorder tend to be smaller than boys without obsessive-compulsive symptoms.

It is possible that some neuroendocrine factor in obsessive-compulsive disorder causes slower growth of the child and mediates behavioral abnormalities. In theory, such an alteration could result in slow growth, late onset of puberty, and obsessive-compulsive symptoms. This hypothesis is particularly intriguing in light of the reported improvement in obsessive symptoms after the administration of antiandrogens (13) and the high rate of postpartum obsessive-compulsive disorder (S. Rasmussen, personal communication). Alternatively, a behavioral abnormality secondary to obsessive-compulsive disorder, such as altered eating patterns or less active life style, could account for the differences. This seems unlikely as the effect was not seen for the comparison group with psychiatric diagnoses other than obsessive-compulsive disorder, which included boys with anxiety disorders. There were only 16 boys in the comparison group with other psychiatric diagnoses; thus, the lack of growth alteration does not rule out the possibility that anxiety per se produces some altered growth pattern. Of greater theoretical interest is the reported association between anorexia nervosa and obsessive-compulsive disorder (14), which again hints at a possible underlying neuroendocrine dysfunction.

These results confirm clinical impressions but raise more questions than they answer. Does obsessive-compulsive disorder affect growth in some way? Does a common defect cause delayed growth and obsessive-compulsive disorder, such as a hormonal dysfunction, a toxic or infectious insult, or a genetic susceptibility to slow pubertal growth and obsessive-compulsive disorder?

Ongoing neuroendocrine research with a clinical sample of adolescents with obsessive-compulsive disorder is needed to address these questions.

REFERENCES

1. Rapoport JL (ed): Obsessive Compulsive Disorder in Childhood and Adolescence. Washington, DC, American Psychiatric Press, 1989
2. Judd L: Obsessive-compulsive neurosis in children. *Arch Gen Psychiatry* 1965; 12:136-143
3. Hollingsworth C, Tanguay P, Grossman L, et al: Long-term outcome of obsessive-compulsive disorder in childhood. *J Am Acad Child Psychiatry* 1980; 19:134-144
4. Pauls DL, Towbin KE, Leckman JF, et al: Gilles de la Tourette's syndrome and obsessive-compulsive disorder: evidence supporting a genetic relationship. *Arch Gen Psychiatry* 1986; 43:1180-1182
5. Rapoport JL, Wise SP: Obsessive-compulsive disorder: evidence for basal ganglia dysfunction. *Psychopharmacol Bull* 1988; 24:380-384
6. Insel TR, Murphy DL: The psychopharmacological treatment of obsessive-compulsive disorder: a review. *J Clin Psychopharmacol* 1981; 1:304-311
7. Jenike MA, Baer L, Minichiello WE (eds): Obsessive-Compulsive Disorders: Theory and Management. Littleton, Mass, PSG, 1986
8. Leonard H, Swedo S, Rapoport JL, et al: Treatment of childhood obsessive-compulsive disorder with clomipramine and desmethylimipramine: a double-blind crossover comparison. *Psychopharmacol Bull* 1988; 24:93-95
9. Whitaker A, Davies M, Shaffer D, et al: The struggle to be thin: a survey of anorectic and bulimic symptoms in a nonreferred adolescent population. *Psychol Med* (in press)
10. Berg C, Whitaker A, Davies M, et al: The survey form of the Leyton Obsessional Inventory—Child Version: norms from an epidemiological study. *J Am Acad Child Adolesc Psychiatry* 1988; 27:759-763
11. Flament M, Whitaker A, Rapoport J, et al: Obsessive-compulsive disorder in adolescence: an epidemiological study. *J Am Acad Child Adolesc Psychiatry* 1988; 27:764-771
12. SAS User's Guide: Statistics, version 5. Cary, NC, SAS Institute, 1985
13. Casas M, Alvarez E, Duro P, et al: Antiandrogenic treatment of obsessive-compulsive neurosis. *Acta Psychiatr Scand* 1966; 73:221-222
14. Kasvikis Y, Tsakiris F, Marks I, et al: Women with obsessive compulsive disorder frequently report a past history of anorexia nervosa. *Int J Eating Disorders* 1986; 5:1069-1075

Patterns of Contagion in Self-Mutilation Epidemics

Paul M. Rosen, Ph.D., and Barent W. Walsh, D.S.W.

Contagion of self-mutilation was studied in a treatment program for disturbed adolescents. Statistical analyses and a sociogram revealed that 1) episodes of contagion were significantly associated with specific pairs of subjects, and 2) a few subjects were identified as being at the center of most of the contagion activity.
(Am J Psychiatry 1989; 146:656-658)

Self-mutilation has been described by many (1-6) as contagious or epidemic within treatment programs. This phenomenon of self-mutilation contagion has generally been defined as the infliction of self-injury by one individual and imitation by others in the immediate environment. Such episodes of contagion are a serious problem because they generally create havoc in treatment settings. In response to contagion episodes, patients tend to become agitated and fearful, while staff report feeling helpless and demoralized.

Although we previously demonstrated that self-mutilation occurs in statistically significant clusters or bursts (1), to our knowledge, no one has gone beyond this basic discovery. The specific interpersonal factors in the initiation and maintenance of contagion episodes have not yet been studied empirically.

Other writers have speculated that self-mutilation contagion is precipitated by a variety of social or psychological antecedents. For example, Stanton and Schwartz (7) contended that problems in staff communication led to "collective disturbances" in behavior among patients. These collective responses included multiple acts of self-harm. In a similar vein, Crabtree and Grossman (8) emphasized institutional coerciveness as a contributor to contagion. They noted a marked reduction in self-mutilation among patients when a locked ward was transformed into an open-door unit. They believed that this change enhanced staff morale and patient dignity, thereby effecting a more benign ward environment. Ross and McKay (6) employed a more psychological perspective in discussing self-mutilation contagion in a training school for

delinquent girls. They interpreted outbreaks of self-mutilation to be primitive forms of communication. They indicated that acts of mutual cutting were intended to express anger or jealousy and to demonstrate affection.

Mindful of these previous reports, we began this study by reviewing our clinical impressions and observations of several contagion episodes. Our conclusion was that specific dyads of patients tended to be involved in the bursts of self-mutilation. The contagion episodes rarely included all or even most of the patients within the treatment setting. Rather, the contagion appeared to occur within a small, established network of closely linked peers. We believed that if we could verify these informal observations using empirical methods, progress could be made in preventing or treating contagion episodes.

Our research hypothesis, therefore, was that self-mutilation contagion would occur repeatedly for specific dyads within the patient population. We predicted that these patient interactions would occur nonrandomly.

METHOD

All subjects in the study were patients at the Community Treatment Complex in Worcester, Mass., a long-term treatment and educational facility for seriously disturbed teenagers. The subjects attended the same academic high school and after-school treatment program 5 days per week. In addition, most lived in residential programs operated by the Community Treatment Complex. Thus, the subjects in the study were exposed to each other for many hours each day—which is a logical prerequisite for contagion.

There were two criteria for the inclusion of subjects in the study: 1) the subjects had to have mutilated themselves at least once while in care, and 2) they had to have been in care for the entire academic year during which the study was conducted. (This ensured that the subjects had extended exposure to each other.) Of the 35 patients in care during the 10-month study period, 12 met these two criteria. These subjects ranged in age from 15 to 21 years, and their mean age was 17.6 years. The sample consisted of 11 girls and one boy. The psychiatric diagnoses for the subjects were major affective disorder (N=7), borderline personality

Received April 1, 1988; revisions received Aug. 18 and Oct. 20, 1988; accepted Nov. 16, 1988. From the Community Treatment Complex, Worcester. Address reprint requests to Dr. Rosen, Community Treatment Complex, 340 Main St., Suite 915, Worcester, MA 01608.

Copyright © 1989 American Psychiatric Association.

disorder (N=3), schizoaffective illness (N=1), and atypical psychosis (N=1).

For 10 months we collected data on all incidents of self-mutilation. The data were compiled by a research assistant from written reports completed daily by the staff who provided the direct care. None of the staff involved in data collection or analysis was aware of the purpose of the study. Interrater reliability was evaluated with kappa, which is a coefficient of agreement between two observers using a nominal scale ($\kappa = 0.80$, $p < 0.001$).

RESULTS

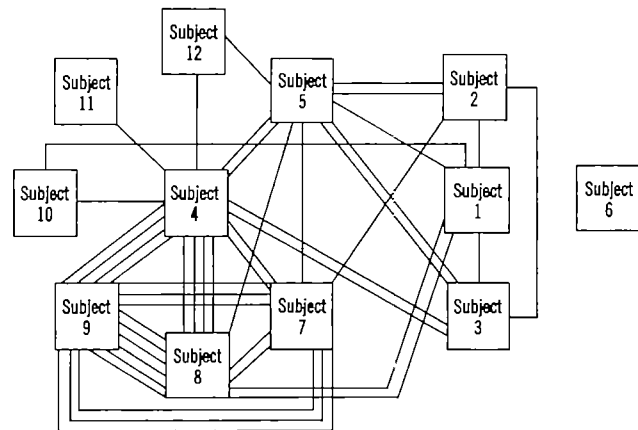
During the 10-month data collection period, 80 acts of self-mutilation were performed by the 12 subjects. The number of incidents per subject ranged from one to 17, and the mean number per subject was 6.7.

Self-mutilation contagion was defined as two or more acts of self-mutilation that involved two or more individuals and occurred on the same day or consecutive days. There were 46 instances of contagion during the 10-month period.

The data were analyzed with 11 independent chi-square analyses. The tests were performed sequentially, beginning with the subject who was involved in the most contagion incidents. This first chi-square test examined the distribution of contagion events between this subject and the other 11 subjects (1×11 contingency table). The next chi-square test was conducted for the subject who was involved in the second highest number of contagion incidents, but the data for the first subject were omitted (1×10 contingency table). This procedure was followed for each succeeding subject, which resulted in the 11 independent chi-square tests. By following this procedure, it was possible to sum the obtained chi-square values for all the tests to obtain an overall value. This procedure resulted in a more powerful test of significance to determine if the self-mutilation occurred in nonrandom fashion. The overall value was significant ($\chi^2 = 75.5$, $df = 55$, $p < 0.05$), supporting the research hypothesis of the study.

In addition to the statistical analyses, we devised a sociogram to illustrate the contagion of self-mutilation from one subject to another. This sociogram, presented in figure 1, shows graphically that certain pairs of subjects were repeatedly involved in the same episodes of self-mutilation contagion. Subjects 8 and 9, for example, were involved in six of the same episodes. Of particular interest is subject 4, who was involved in the most episodes of contagion (17 incidents) with the highest number of other patients (eight patients). This subject seemed to be a prime source of contagion within the treatment program. Other subjects (e.g., 6 and 11) were seldom or never involved in self-mutilation contagion.

FIGURE 1. Sociogram of Contagious Self-Mutilation Over 10 Months in an Adolescent Treatment Program*



*Self-mutilation contagion was defined as two or more acts of self-mutilation that involved two or more individuals and occurred on the same day or consecutive days. Each line connecting two squares represents an incident of contagion.

DISCUSSION

These findings suggest that contagion may be best understood in terms of dyadic or small-group interactions. Contagious self-mutilation may be appropriately viewed as a concrete display of affinity between two people. Our clinical observations regarding these dyadic relationships reveal a general pattern: 1) the individuals involved are usually highly enmeshed, 2) they have difficulty with more conventional forms of intimacy, and 3) they find deviant acts, such as shared self-mutilation, to be compelling and exciting. These individuals appear to use self-mutilation to communicate feelings and to ensure a tight, although temporary, bond within a relationship.

The results suggest that interventions to stop or reduce contagion may be most effective when they strategically target specific dyads or small groups rather than the whole milieu. For example, as the sociogram indicates, when subject 9 commits self-mutilation, subjects 4, 7, and 8 are clearly most at risk to follow suit. As a result, treatment strategies might target this subgroup to interrupt or limit a contagion sequence. One or two patients may be especially influential in instigating contagion episodes. For example, in this study subject 4 was at the center of a substantial number of self-mutilation incidents. It became clear that isolating subject 4 when she began to mutilate herself would markedly reduce imitation by the subjects affiliated with her.

We used statistical analysis and a sociogram to better explain episodes of self-mutilation contagion. The sociogram is a simple but useful tool for identifying dysfunctional dyads that "collaborate" in self-mutilation. Such dyads can be helped to express emotion and negotiate intimacy in more normative ways. When this

positive approach is not successful, it may be necessary to isolate a key instigator from the rest of the group.

It is important to refrain from making cause-and-effect statements regarding the data presented in this study. It is neither possible nor accurate to say that one patient causes another to commit self-mutilation. More research is necessary to identify the specific variables responsible for contagion and to determine if these results can be generalized beyond a program for disturbed adolescents. Ultimately, self-mutilation contagion is likely to be best understood as an interaction of individual psychopathology with dysfunctional relationships in a given social context.

REFERENCES

1. Walsh BW, Rosen P: Self-mutilation and contagion: an empirical test. *Am J Psychiatry* 1985; 142:119-120
2. Walsh BW, Rosen PM: *Self-Mutilation: Theory, Research and Treatment*. New York, Guilford Press, 1988
3. Menninger KA: A psychoanalytic study of the significance of self-mutilations. *Psychoanal Q* 1935; 4:408-466
4. Matthews PC: Epidemic self-injury in an adolescent unit. *Int J Soc Psychiatry* 1968; 14:125-133
5. Simpson MA: The phenomenology of self-mutilation in a general hospital setting. *Can Psychiatr Assoc J* 1975; 20:429-433
6. Ross RR, McKay HB: *Self-Mutilation*. Lexington, Mass, DC Heath, 1979
7. Stanton A, Schwartz M: *The Mental Hospital*. New York, Basic Books, 1954
8. Crabtree LH, Grossman WK: Administrative clarity and redefinition for an open adolescent unit. *Psychiatry* 1974; 37:350-359

Prevalence and Presentation of Depressive Illness in a Primary Health Care Setting in Kenya

Manohar Dhadphale, Ph.D., F.R.C.Psych., Graham Cooper, M.R.C.A.P.,
and Lesley Cartwright-Taylor, M.Sc., Ph.D.

Using a two-stage screening procedure, ICD-9 diagnostic criteria, and the Hamilton Rating Scale for Depression, the authors diagnosed depressive disorders in 81 (9.2%) of 881 patients in a primary care setting in Kenya. All depressed patients had somatic symptoms, and all of the 27 depressed patients assessed with the Hamilton scale scored higher than 2 on the work and activities item. These findings contradict the earlier reports that Africans do not admit to being depressed. Nearly one-third of the depressed patients were moderately or severely ill and would have benefited from psychiatric assessment and treatment.

(Am J Psychiatry 1989; 146:659-661)

Since Carothers' report (1) of an extremely low prevalence of depression among Africans, many African scientists (2-5) have produced evidence that depression occurs almost as frequently in Africa as elsewhere. The subject of frequency and presentation of depression became a central issue at the 4th Pan-African conference (6), where leading researchers from almost all of sub-Saharan Africa gathered to express their views and relate their experiences. During the early 1970s the concepts of "masked" depression (7) and depressive equivalents (8) were advanced to elucidate the presentation of depressive disorders in terms of physical complaints. These possibilities did not answer the basic question of whether depression really had been increasing among Africans since the end of imperial regimes. Prince put forward various thought-provoking arguments based on his own experience in Africa and review of the local literature (cited by Carothers [9]).

According to Prince, the major factors in the increase of reports of depression were change in diagnostic modes, the hiring of Africans for more responsible jobs, increased recognition of "masked" depression, and a

shift of research focus from mental hospitals to the community. African psychiatrists now generally agree that depression is as common among the inhabitants of this continent as elsewhere in the world.

However, there are still controversies about the actual prevalence and presentation of depressive disorders, as almost all such cases are identified in primary health clinics, and most primary health workers are not physicians and hitherto have had only marginal experience in the recognition of psychiatric illness. Many primary clinic staff can easily identify schizophrenic, manic, or other violent psychiatric patients but fail to confidently diagnose most of the neurotic disorders (Dhadphale, unpublished work, 1984).

In spite of the availability of trained physicians in primary care settings in North America, much psychiatric morbidity still remains unrecognized (10). Therefore, efforts are being made there to increase primary care physicians' recognition of mental illness by training family practice residents in interviewing techniques and providing physicians with feedback on patients' psychosocial screening scores (11). Such interventions have been reported to improve assessment, especially in depressive disorders (12).

To provide reliable data on this important subject, a nationwide study to estimate the prevalence of psychiatric morbidity in Kenya was undertaken in 1980 and was completed in 1983 (Dhadphale, 1984). Only important aspects of the prevalence and presentation of depression will be highlighted here.

METHOD

This work was a part of a nationwide study on the prevalence of mental illness in Kenya. The details of the methods were described by Dhadphale et al. (13).

The subjects were 881 patients who were randomly selected from the outpatient queues in four district hospitals in various parts of the Republic of Kenya. Psychiatric assessment was conducted in two stages: the Self-Reporting Questionnaire (2) was used for screening, and the Standardized Psychiatric Interview (14) was used to confirm possible cases. Patients who met the diagnostic criteria for ICD-9 categories 296.1 and 300.4 were considered depressed. According to

Received March 16, 1988; revision received Oct. 20, 1988; accepted Nov. 16, 1988. From the Department of Psychiatry, University of Nairobi, and the Medical Research Centre, Ciba-Geigy, Nairobi, Kenya. Address reprint requests to Dr. Dhadphale, 25 Woodville Rd., London NW11 9TP, U.K.

Copyright © 1989 American Psychiatric Association.

TABLE 1. Prevalence of Depression Among 881 Primary Care Patients in Kenya

Patient Variable	N	Percent of		
		Total Sample	Psychiatric Cases	Depressed Patients
Had psychiatric disorder according to Standardized Psychiatric Interview	220	25.0		
Met ICD-9 criteria for depression	81	9.2	36.8	100.0
Category 300.4 (<i>DSM-III-R</i> dysthymia)	70	7.9	31.8	86.4
Category 296.1 (<i>DSM-III-R</i> major depression)	11	1.2	5.0	13.6
Scored >2 on Hamilton depression scale item ^a				
Work and activities	27	—	—	100.0
Depressed mood	26	—	—	96.3
Anxiety (somatic and psychic)	19	—	—	70.3
Hypochondriasis	18	—	—	66.7
Paranoid symptoms	15	—	—	55.6
Loss of weight	13	—	—	48.1
Somatic symptoms	12	—	—	44.4
Psychomotor agitation	10	—	—	37.0
Insomnia, early and middle	7	—	—	25.9
Insomnia, late (early awakening)	6	—	—	22.2
Diurnal variation	5	—	—	18.5
Suicide	3	—	—	11.1
Insight	3	—	—	11.1
Genital symptoms	2	—	—	7.4
Feelings of guilt	1	—	—	3.7
Depression severity ^b				
Severe	2	—	—	2.5
Moderate	22	—	—	27.2
Mild	57	—	—	70.4

^aThe percents are based on the 27 depressed patients who were assessed with the Hamilton scale.

^bClinical ratings of symptom severity based on criteria of Shepherd et al. (16).

DSM-III-R, 296.1 refers to major depression and 300.4 is dysthymia. One-third of the 81 depressed patients ($N=27$) were given the Hamilton Rating Scale for Depression (15). Any item on which a patient scored higher than 2 was considered present. A frequency distribution of important symptoms (rated higher than 2) was drawn up to show the percentage of patients with each of these complaints.

RESULTS

As shown in table 1, 25.0% of the 881 randomly selected primary care patients were found to have psychiatric disorders. Over one-third of the patients with psychiatric illnesses were depressed, and nearly one-third of the depressed subjects were moderately or severely ill. All of the depressed patients had somatic symptoms. Table 1 also contains the prevalences of individual depressive symptoms in the 27 patients assessed with the Hamilton depression scale. All 27

scored higher than 2 on the work and activities item, and 26 scored higher than 2 on depressed mood.

DISCUSSION

Prevalence

Depression was found in about 9% of the primary care patients in our Kenyan sample and was the most frequent single psychiatric diagnosis. Although 70% of these diagnoses were "minor," this finding is not insignificant. The fact that a subject has traveled several kilometers to a primary health clinic and has spent money and time to see a primary health worker reflects a keen desire and need to attend a health facility. The research instruments we used are likely to pick up mainly moderate or severe cases. It is our view that any ailment which brings the patient to a health facility should be considered more than a mild illness. The underlying disorder should be correctly identified, and appropriate treatment should be given so that the clinic load of chronic psychiatric morbidity (16), which often remains unidentified, can be reduced. Our results indicate a prevalence for depressive disorder of one in 11 patients. If one adds other neurotic disorders, such as anxiety and phobic neurosis, then the prevalence doubles—to almost 1 in 5. Often in the primary care setting the health worker is unable to distinguish between a primary anxiety disorder and depression. We believe that the label "anxiety-depression syndrome" (17) would help the primary health worker make a reasonably correct diagnosis. Many antidepressant drugs have anxiolytic properties, and nosological distinctions should be left to the research worker or expert, while the primary health worker can effectively identify, diagnose, and treat the clinic attenders who present with mixed anxiety-depressive symptoms (18). Similarly, in a multicultural international study, Leff (19) observed a high correlation between anxiety and depression in the participants from developing countries, and he noted that feelings of anxiety and depression are not always differentiated in these countries as they are in the developed world. However, anxiety and depression should be precisely delineated according to *DSM-III* or *ICD* definitions if a trained physician is available at the primary care level. Such a distinction is desirable for international or multicultural comparisons.

Presentation

The general belief among European psychiatrists and even some indigenous psychiatrists that depression is rarely seen among the native population in Africa began in the colonial era. This myth was based on early work in institutions, where most of the "mad" patients were admitted and where all the colonial psychiatrists were based (1, 20). It is true that few de-

pressed native patients were admitted to mental hospitals, as their symptoms did not fit the traditional presentation of "madness" and only manic, schizophrenic, or other violent patients were readily identified by the chiefs or local inhabitants and promptly sent to mental asylums. It is also true that even today depressed individuals present themselves to primary health clinics with physical complaints or communicate with the health worker in a "somatic language"—the only language the patient thinks the health worker can understand! Even in Western countries, leading research workers are aware of the substantial degree of "hidden psychiatric morbidity" (21). Jones and Vischi (22), in a study of American family physicians, observed that almost 80% of the psychiatric cases were not recognized.

Because of the overwhelming numbers of patients with serious tropical diseases in Africa, until recently the psychiatric input in medical training was negligible. Moreover, primary health workers had little time to deal with patients who had hidden psychiatric morbidity. In our settings, these subjects often were labeled "chronic," "hypochondriacal," or "neurotic," and the clinicians soon lost interest. This led to a cycle of endless referrals from clinic to clinic or futile investigations. Almost all such cases received symptomatic treatment alone.

We found that all of the depressed subjects who were assessed with the Hamilton scale scored higher than 2 on the work and activities item, and all the depressed subjects had somatic symptoms. In many cultures exact vernacular equivalents of certain scientific terms do not exist (23), and this makes it difficult for the investigator to ask questions the patient can readily understand. Therefore, the primary health worker must inquire about the patient's emotional state in simple colloquial terms rather than in scientific jargon.

The present work strongly indicates that depression is widely prevalent among primary care attenders in Kenya, and although somatic symptoms dominate the clinical presentation, a health worker can invariably find evidence of psychological or emotional phenomena of depression, as was noted in Kenya by Acuda (24) and one of us (Dhadphale, 1984).

REFERENCES

1. Carothers JC: A study of mental derangement in Africans, and an attempt to explain its peculiarities, more especially in relation to the African attitude to life. *J Ment Sci* 1947; 93:548-597
2. Harding TW, De Arango MV, Baltazar J, et al: Mental disorders in primary health care: a study of their frequency and diagnosis in four developing countries. *Psychol Med* 1980; 10: 231-241
3. Otsyula W, Rees P: Occurrence and recognition of minor psychiatric illness among outpatients at the Kenyatta National Hospital. *East African Med J* 1972; 49:825-829
4. Giel R, Van Luijk JN: Psychiatric morbidity in a small Ethiopian town. *Br J Psychiatry* 1969; 115:149-162
5. Orley J, Wing JK: Psychiatric disorders in two African villages. *Arch Gen Psychiatry* 1979; 36:516-520
6. Asuni T: Introductory remarks, in *Recognition of Depression in the African: Proceedings of the Fourth Pan-African Congress on Psychiatry*. Edited by Asuni T. Abidjan, Ivory Coast, Ciba-Geigy, 1975
7. Kielholz P: Opening address: psychosomatic aspects of depressive illness—masked depression and somatic equivalents, in *Masked Depression*. Edited by Kielholz P. Bern, Switzerland, Hans Huber, 1973
8. López Ibor JJ: Depressive equivalents. *Ibid*
9. Carothers JC: *Mind of Man in Africa*. London, Tom Stacey, 1972, p 159-160
10. Kessler LG, Cleary PD, Burke JD Jr: Psychiatric disorders in primary care: results of a follow-up study. *Arch Gen Psychiatry* 1985; 42:583-587
11. Schulberg HC, Burns BJ: Mental disorders in primary care: epidemiologic, diagnostic, and treatment research directions. *Gen Hosp Psychiatry* 1988; 10:79-87
12. Linn L, Yager J: The effect of screening, sensitization, and feedback on notation of depression. *J Med Educ* 1980; 55:942-949
13. Dhadphale M, Ellison RH, Griffin L: The frequency of psychiatric disorders among patients attending semi-urban and rural general outpatient clinics in Kenya. *Br J Psychiatry* 1983; 142: 279-283
14. Goldberg DP, Cooper B, Eastwood MR, et al: A standardized psychiatric interview for use in community surveys. *Br J Prev Soc Med* 1970; 24:18-23
15. Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56-62
16. Shepherd M, Cooper B, Brown AC, et al: *Psychiatric Illness in General Practice*. London, Oxford University Press, 1981
17. Hamilton M: Combined anxiety-depressive states, in *Anxiety Factors in Comprehensive Patient Care*. Edited by Lindford-Rees W. New York, Excerpta Medica, 1973
18. Dhadphale M: Management of depression in general practice. *East African Med J* 1981; 58:715-719
19. Leff J: Culture and differentiation of emotional states. *Br J Psychiatry* 1973; 123:299-306
20. Gordon HL: An enquiry into the correlation of civilization and mental disorders in the Kenyan native. *East African Med J* 1936; 12:327-335
21. Goldberg DP, Blackwell B: Psychiatric illness in general practice: a detailed study using a new method of identification. *Br Med J* 1970; 2:439-443
22. Jones KR, Vischi TR: Impact of Alcohol, Drug Abuse and Mental Health Treatment on Medical Care Utilization: A Review of the Research Literature. *Med Care* 1979; 17(Dec suppl), p 12
23. Sartorius N: Cross-cultural research on depression. *Psychopathology* 1987; 19(2):6-11
24. Acuda SW: Presentation of psychiatric illness in East Africa. *Postgraduate Doctor (Africa)*, January 1982, pp 20-23

Psychopathology in Patients With Wilson's Disease

Alice Medalia, Ph.D., and I. Herbert Scheinberg, M.D.

The authors used the MMPI to assess psychopathology in neurologically impaired and neurologically asymptomatic patients with Wilson's disease. Neurologically impaired patients showed more psychopathology on the schizophrenia and depression scales and had a significantly higher rate of severe depression.

(Am J Psychiatry 1989; 146:662-664)

Wilson's disease is an autosomal recessively inherited disease of copper metabolism with a prevalence of about 30 per 1,000,000 in all ethnic and geographic groups. About 20% of patients present initially with psychiatric disturbances; almost all others present with hepatic or neurological disease. In his original monograph (1), Wilson discussed some of the psychological symptoms that these patients manifest. Although he later wrote that "too much must not be made of these psychotic [sic] symptoms" (2), subsequent research (3-5) has shown that psychological illness, ranging in severity from mild to severe, is indeed an important aspect of Wilson's disease.

Since copper, whose toxicity causes all of the neurological manifestations of Wilson's disease, is ubiquitous in the brain (6), it is reasonable to suppose that copper toxicity may underlie, at least in part, the psy-

chiatric disturbances seen. If this were the case, psychopathology would be expected to be more severe in patients with Wilson's disease who are neurologically affected than in those who are asymptomatic. We tested this hypothesis by administering the MMPI to groups of patients with and without neurological impairment.

METHOD

We examined 24 patients who were diagnosed as having Wilson's disease and who were in treatment with one of us (I.H.S.) or with Dr. I. Sternlieb. The diagnosis of Wilson's disease was made on the basis of a demonstrated deficiency of ceruloplasmin (less than 20 mg/dl) and the presence of Kayser-Fleischer rings or an excess of hepatic copper (more than 250 μ g per gram of dry liver) or both (3).

Sixteen patients (nine men and seven women) had neurological disease and comprised group one. Eight patients (two men and six women) whose neurological examination had always been normal comprised group two. The mean \pm SD ages in groups one and two were 31.75 ± 6.31 and 26.5 ± 4.72 , respectively. The two groups differed in the number of years they had been diagnosed with Wilson's disease and in the way they initially presented for medical treatment. Patients in group one had been diagnosed with Wilson's disease for a mean of 8.7 ± 8.2 years, but patients in group two had had the diagnosis for a mean of 17.3 ± 3.0 years. Four patients in group one presented with neurological symptoms, five with psychiatric symptoms, five with both neurological and psychiatric symptoms, and two with hepatic symptoms. Four patients in group two presented with hepatic symptoms, one presented with hepatic symptoms and very minor psychiatric symptoms, and three were asymptomatic and had been diagnosed in early childhood because they were siblings of patients with Wilson's disease. "Psychiatric" was defined for these purposes as any change in behavior

Received March 16, 1988; revision received Oct. 20, 1988; accepted Nov. 16, 1988. From the Department of Psychiatry and the Division of Genetic Medicine, Department of Medicine, Albert Einstein College of Medicine/Montefiore Hospital Medical Center, Bronx, N.Y. Address reprint requests to Dr. Medalia, Bronx Municipal Hospital Center, Rm. 1009, Pelham Parkway and Eastchester Rd., Bronx, NY 10461.

Supported in part by the National Center for the Study of Wilson's Disease.

The authors thank Dr. I. Sternlieb for referring patients to the study, Dr. Igor Galyinker for assisting with data collection, and Dr. Jonathan Tobin for statistical consultation.

Copyright © 1989 American Psychiatric Association.

noted by family, teachers, or close acquaintances. Fourteen patients in group one had a history of psychiatric problems; but only one patient in group two had such a history.

We reviewed records to determine the hepatic copper levels of patients on initial presentation. Patients in group one had lower mean hepatic copper levels (565.2 ± 428.5 μg per gram of dry liver) than patients in group two (mean \pm SD = 972.5 ± 477.3). Although statistically insignificant according to one-tailed *t* test ($p < 0.36$), the difference in group means may reflect the process by which copper first saturates the liver and then is released into the blood stream, whence it diffuses into the nervous system and other organs (3). As was seen in the patients in group one, this process decreases hepatic copper but leads to copper toxicosis in other systems.

The MMPI, which was used to measure psychopathology, was completed by each patient working alone and was scored by computer. All patients provided informed consent.

The MMPI yields scores on 10 clinical scales. We report here scores on the four scales that measure symptoms associated with major psychiatric disorders (*DSM-III-R* axis I): schizophrenia, depression, paranoia, and hypomania. Higher scores indicate greater psychopathology. To obtain a quantitative index of psychopathology from the MMPI, it is accepted clinical practice to average an individual's scores on eight of the 10 clinical scales (hypochondriasis, depression, hysteria, psychopathic deviant, paranoia, psychasthenia, schizophrenia, and hypomania). This score will be referred to as the psychopathology index.

RESULTS

One-tailed *t* tests indicated that neurologically impaired patients (group one) scored significantly higher than neurologically asymptomatic patients (group two) on the schizophrenia scale (group one: 64.94 ± 20.61 ; group two: 47.75 ± 6.86 ; $t = 3.026$, $df = 22$, $p < 0.003$), the depression scale (group one: 63.25 ± 18.67 ; group two: 52.5 ± 5.58 ; $t = 2.12$, $df = 19.5$, $p < 0.02$), and the psychopathology index (group one: 60.79 ± 13.08 ; group two: 52.27 ± 3.56 ; $t = 2.43$, $df = 18.9$, $p < 0.01$). On the hypomania scale the means for groups one and two were 60.00 ± 15.34 and 51.8 ± 7.62 , respectively ($p < 0.08$). On the paranoia scale the means for groups one and two were 61.63 ± 14.68 and 56.63 ± 9.1 , respectively ($p < 0.19$). The Bonferroni adjustment indicated that *p* values less than or equal to 0.01 were significant. Thus, the group differences on the schizophrenia scale and the psychopathology index remained significant and the difference on the depression scale strongly approached significance.

The prevalence of scores of 70 or greater, generally considered to reflect moderate to severe psychopathology (7), was examined for the two groups. Fisher's exact test was used to compare the proportion of

TABLE 1. Neurologically Impaired and Neurologically Asymptomatic Patients With Wilson's Disease Who Scored 70 or More on Selected MMPI Scales

MMPI Scale	Neurologically Impaired (N=16)		Neurologically Asymptomatic (N=8)		p ^a
	N	%	N	%	
Depression	7	44	0	0	0.03
Schizophrenia	5	31	0	0	0.10
Hypomania	5	31	0	0	0.10
Paranoia	3	19	1	13	0.59
Psychopathology index	3	19	0	0	0.27

^aOne-tailed Fisher's exact test.

high scores in the two groups. Group one had a significantly higher rate of scores of 70 or more on the depression scale ($p < 0.03$, one-tailed). The rates of high scores on the MMPI scales for both groups are listed in table 1.

DISCUSSION

These results indicate that patients with Wilson's disease who have neurological symptoms are more likely to exhibit clinically significant psychopathology than are neurologically asymptomatic patients. The neurologically impaired patients scored significantly higher on the schizophrenia and depression scales and the psychopathology index. Furthermore, there was a particularly high rate of depression in the neurologically impaired patients with Wilson's disease: 44% of these patients had scores of 70 or more, indicating moderate to severe depression and serious problems coping with daily activities. None of the neurologically asymptomatic patients had a score over 60 on the depression scale.

Moreover, five of the neurologically impaired patients had scores of 70 or more on the schizophrenia scale, whereas the highest score among the neurologically asymptomatic patients on this scale was 57. On the psychopathology index, three neurologically impaired patients had scores of 70 or more, whereas no neurologically asymptomatic patient had a score over 57.

These results indicate that there is an association between psychopathology and neurological symptoms in Wilson's disease. Clinical history and observation of the patients confirm the MMPI results. Only one neurologically asymptomatic patient ever manifested behavioral changes, and these were quite mild. That individual was noted to be less alert in his first-grade class; hepatic disease was subsequently diagnosed. In contrast, 14 of the 16 neurologically symptomatic patients had a history of substantial behavioral problems. At least three of these patients required psychiatric

hospitalization, one for schizophreniform psychosis and two for affective disorders. Another five patients had mild depression. Seven of the neurologically impaired patients had histories of erratic, impulsive, or bizarre behavior, including violence, excessive emotional lability, and acting out. At least 12 of the neurologically impaired patients had received psychiatric or psychological assessment and/or treatment.

It is reasonable to conclude that psychopathology in patients with Wilson's disease is caused both by copper-induced cerebral pathology and by reactions to the motor disorders. The latter can interfere so severely with speech and the ability to eat, write, and walk that it is difficult or impossible to function normally in society or to maintain satisfying interpersonal relationships.

REFERENCES

1. Wilson SAK: Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. *Brain* 1912; 43:295-507
2. Wilson SAK: Progressive lenticular degeneration, in *Neurology*. Edited by Bruce AN. Baltimore, Williams & Wilkins, 1955
3. Scheinberg IH, Sternlieb I: *Wilson's Disease*. Philadelphia, WB Saunders, 1984
4. Scheinberg IH: The neurotoxicity of copper, in *Metal Neurotoxicity*. Edited by Bondy SC, Prasad KN. Boca Raton, Fla, CRC Press, 1988
5. Scheinberg IH: Psychosis associated with hereditary disorders, in *American Handbook of Psychiatry*, 2nd ed, vol IV. Arieti S, editor-in-chief. New York, Basic Books, 1975
6. Horoupian DS, Sternlieb I, Scheinberg IH: Neuropathological findings in penicillamine-treated patients with Wilson's disease. *Clin Neuropathology* 1988; 2:62-67
7. Graham JR: *The MMPI: A Practical Guide*. New York, Oxford University Press, 1977

Posttraumatic Stress Disorder: A Descriptive Study Supporting *DSM-III-R* Criteria

Anthony Feinstein, M.B.B.Ch., M.R.C.Psych.

Posttraumatic stress disorder, as defined by DSM-III, remains a controversial diagnostic entity. This descriptive study, which was carried out by the author in a war zone, supports the changes made in the criteria in DSM-III-R.

(Am J Psychiatry 1989; 146:665-666)

Controversy still surrounds the concept of post-traumatic stress disorder (PTSD) and its validity as a distinct diagnostic entity. Much of this controversy can be traced to establishing the significance of the "stressor," thus continuing the longstanding stress-vulnerability debate in psychiatric research. *DSM-III-R* has attempted to resolve some of these difficulties by clarifying the nature of the stressor still further and also by removing the subdivision of PTSD into acute and chronic or delayed subtypes. The descriptive study reported here supports the latter revision. To my knowledge, there has been no similar report of a longitudinal, descriptive study carried out among soldiers actively engaged in combat.

During my obligatory national service I was assigned to act as psychiatric medical officer in the operational area of Namibia (the area of Namibia in which military operations were regularly pursued). For a period of 1 month I had to undertake daily patrols with a 16-man counterinsurgency unit.

The unit consisted of 17 men, 15 in their 20s and two in their early 40s. Seven of the men were married. Both official language groups (i.e., English and Afrikaans), with their associated cultural differences, were represented in the sample; educational status varied from university level to various grades of school qualification. Only two men were military recruits; the rest were career policemen or soldiers. Only three of the men had had previous combat exposure. No soldier had a history of psychiatric illness.

Received Feb. 26, 1988; revision received Oct. 20, 1988; accepted Nov. 17, 1988. From the Department of Psychiatry, Royal Free Hospital, London. Address reprint requests to Dr. Feinstein, Department of Neuropsychiatry, National Hospital for Nervous Diseases, Queen Square, London WC1N 3BG, England.

The author thanks Dr. M. Ron for her help in preparing this paper.

Copyright © 1989 American Psychiatric Association.

The patrols were highly stressful. There was constant danger from land mines, ambushes, and snipers; the heat was intense; and it was difficult to distinguish noncombatants from the enemy. All unit members were rated as having moderate or high combat exposure on a modified version of a scale devised by Laufer et al. (1). (I used the scale to retrospectively rate the unit members.) On the day after my arrival, at midday, our patrol was ambushed in a local village. For 30 minutes we were caught in an intense crossfire involving mortars, missiles, and automatic weapons. Casualties were sustained on both sides. In addition to treating shrapnel and burn wounds while under fire, I had to sedate a young sergeant with intravenous diazepam after a missile had penetrated the armor of his troop carrier, causing a severe leg wound.

The scene after the ambush was one of carnage. The village was on fire, dismembered bodies made identification impossible, and the local population had fled. Our wounded could be evacuated by helicopter only after the fighting had abated.

THE STUDY

The next day I decided to undertake a descriptive study, using a checklist of symptoms derived from the *DSM-III* criteria for PTSD. Fourteen men, including myself, had been involved in the ambush. An additional three men had been left at the base camp and had listened to the entire battle over their two-way radio. They were included in the study. All the men were interviewed on the day after the ambush and were followed up over a period of 1 month; the symptom checklist was administered at weekly intervals. If individual symptoms were no longer reported, the men were asked when the symptoms had ceased during the previous week. New symptoms and the recurrence of symptoms were also recorded.

RESULTS

Examination of the results 1 week after the ambush (table 1) revealed that all of the 12 *DSM-III* inclusion criteria were frequently reported. In addition, gastrointestinal symptoms (nausea and epigastric discom-

TABLE 1. PTSD Symptoms Reported 1 Week After an Ambush by 14 Soldiers Caught in the Ambush and Three Other Soldiers

<i>DSM-III</i> Symptom	Total (N=17)	Active Group (N=14)	Passive Group (N=3)
Intensification of symptoms by exposure to events that symbolize or resemble the traumatic event	15	13	2
Hyperalertness or exaggerated startle response	14	13	1
Recurrent and intrusive recollections of the event	13	12	1
Sudden acting or feeling as if the traumatic event were reoccurring, because of an association with an environmental or ideational stimulus	11	11	0
Avoidance of activities that arouse recollection of the traumatic event	10	10	0
Sleep disturbance	9	8	1
Guilt about surviving when others have not, or about behavior required for survival	9	7	2
Memory impairment or trouble concentrating	9	8	1
Recurrent dreams of the event	8	7	1
Markedly diminished interest in one or more significant activities	7	7	0
Constricted affect	5	5	0
Feeling of detachment or estrangement from others	4	3	1

fort) were prominent. For many, the ambush seemed to act as a trigger for unpleasant, intrusive thoughts concerning previous traumatic experiences, fear of mutilation, and imagery of death and dying. On my initial arrival at the base camp, I had found a jovial, easygoing, high-spirited group of young men. After the ambush the atmosphere changed. Complaints of sleeplessness became common. One man became fearful that he would be castrated in a land mine explosion. Another man, who had "frozen" during the battle and not fired a shot, became profoundly depressed and had marked guilt feelings. He isolated himself socially and developed enough symptoms to warrant a *DSM-III* diagnosis of major depression. A third man was subject to obvious nightmares, for he would yell and shout commands in his sleep, further affecting morale.

A *DSM-III* diagnosis of PTSD could have been made for all 14 men involved in the ambush, as well as for one of the men left at the base camp. The disorder persisted for an average of 9 days (range=2–24 days) in 14 of the men. One man had to be evacuated within a week of the ambush because his psychiatric symptoms rendered him unable to function; he was lost to follow-up.

In the weeks after the ambush the daily patrols continued, and the men functioned efficiently despite the

heightened tension. Discipline remained intact, an exception being two instances in which morphine ampuls disappeared from my medical bag.

DISCUSSION

Although symptoms sufficient to diagnose *DSM-III* PTSD were present in every member of the group after the ambush, the group continued to function efficiently. PTSD is typically a chronic and quite debilitating disorder, and so these findings present an anomaly. The revisions to *DSM-III-R* resolve these apparent contradictions, for *DSM-III-R* has introduced a minimum duration of 1 month's symptoms before the full PTSD disorder can be diagnosed. Thus, cognizance has been taken of the fact that normal periods of distress can be expected after major life events, and only the persistence of a certain constellation of symptoms can be regarded as pathological. Sufficient symptoms in our group did not extend beyond 24 days and functioning was not seriously impaired, thus precluding a *DSM-III-R* diagnosis of PTSD.

The development of posttraumatic symptoms in members of the group not actively involved in the ambush is an interesting but not unexpected finding. Their proximity to the action, experience of similar dangerous patrols, and daily contact with survivors of the ambush were all bound to exert some effect.

Care should be taken not to draw too many conclusions from a study involving only 17 men. No baseline frequency of symptoms was available with which to compare symptoms after the ambush. Horowitz et al. (2) have pointed out that a multitude of antecedent variables has made phenomenological descriptions of PTSD exceedingly difficult, and the present study, with differing language, cultural, and educational subgroups, is no exception. In addition, the follow-up period was of short duration. Nothing is known of the men's long-term functioning, and the possibility of a delayed PTSD cannot be excluded.

Notwithstanding these obvious limitations, the results of this study and my personal observations support one of the recent revisions to the *DSM-III* criteria for PTSD. Future research of a longitudinal nature, looking at the natural history of the disorder, would prove useful in further validating *DSM-III-R* criteria.

REFERENCES

1. Laufer RS, Brett E, Gallops MS: Posttraumatic stress disorder reconsidered: posttraumatic stress disorder among Vietnam veterans, in PTSD: Psychological and Biological Sequelae. Edited by van der Kolk BA. Washington, DC, American Psychiatric Press, 1984
2. Horowitz MJ, Wilner N, Kaltreider N, et al: Signs and symptoms of posttraumatic stress disorder. *Arch Gen Psychiatry* 1980; 37:85–92

Prevalence of Posttraumatic Stress Disorder in Wounded Vietnam Veterans

Roger K. Pitman, M.D., Bruce Altman, Psy.D., and Michael L. Macklin, B.A.

Of 156 wounded Vietnam veterans evaluated for posttraumatic stress disorder (PTSD) by a questionnaire and a diagnostic interview in selected cases, 40% had a definite or probable lifetime diagnosis of PTSD. Of the 27 interviewed patients with lifetime PTSD, 81% currently met the PTSD criteria.

(Am J Psychiatry 1989; 146:667-669)

The impact of posttraumatic stress disorder (PTSD) on the Vietnam veteran patient is now well recognized. However, the published epidemiological studies of its prevalence have used only one structured research interview, the Diagnostic Interview Schedule (DIS) (1). One such study (2) estimated the lifetime prevalence of PTSD in Vietnam combat veterans (N=43) as 9% and in wounded Vietnam combat veterans (N=15) as 20%. Another study (3) estimated the lifetime prevalence in combat and noncombat Vietnam veterans combined (N=2,490) as 15%. However, only 2% currently met the criteria for PTSD.

The Structured Clinical Interview for *DSM-III-R* (SCID) is a widely used instrument, a version of which has been created for use with Vietnam veterans (4). The Mississippi Scale for Combat-Related PTSD (5) is a questionnaire that has been validated for Vietnam veterans; a cutoff score of 107 identified veterans with current PTSD with 93% sensitivity and 89% specificity. Agreement between the Mississippi scale and the SCID has been shown to be very good: kappa=0.77 (5). In this study, we used the Mississippi scale to screen a sample of wounded Vietnam veterans for PTSD and then evaluated potential cases further with the SCID.

Received Aug. 16, 1988; revision received Nov. 8, 1988; accepted Nov. 23, 1988. From the Research Service, VA Medical Center, Manchester, N.H., and the Harvard Medical School, Boston, Mass. Address reprint requests to Dr. Pitman, Research Service (151), VA Medical Center, 718 Smyth Rd., Manchester, NH 03104.

Supported by VA Merit Review and Research Career Development Awards to Dr. Pitman.

The authors thank K. Davis and V. Tsou for assistance in data retrieval and Drs. T. Keane, R. Kulka, and W. Schlenger for suggestions.

METHOD

A computer printout of New Hampshire Vietnam war veterans who had service-connected musculoskeletal injuries was obtained from the Veterans Administration (VA). One of us (M.L.M.) reviewed each claims folder to ascertain the source of injury, which in 243 cases proved to be wounds sustained during combat in Vietnam. The sample included all New Hampshire veterans whose claims had been adjudicated by the VA, regardless of treatment status, but not veterans with claims adjudicated solely by a service branch nor veterans without adjudicated claims. The sample did not include veterans with other combat injuries (e.g., head trauma or burns), as the purpose was to study the psychopathological consequences of a representative stressor, arbitrarily chosen to be combat that resulted in musculoskeletal injury. A Mississippi Scale for Combat-Related PTSD questionnaire, along with an explanation of the study, was mailed to each of the 243 potential subjects. Nonresponders were contacted by telephone when possible. One hundred fifty-six (64%) of the veterans responded to the questionnaire. No valid address could be found for 14 veterans, there was no response from 48, and 25 refused to participate.

Twenty-five of the 243 veterans had been rated by the VA as having service-connected PTSD. Each of these patients had received a *DSM-III* or *DSM-III-R* diagnosis of PTSD on the basis of a clinical interview (6) by an experienced, Board-certified psychiatrist. These 25 subjects adjudicated as having service-connected PTSD were not interviewed again. Rather, those with Mississippi scale scores of 107 or higher were classified as definite cases of PTSD; those who scored below 107 (possibly representing past cases) or for whom no Mississippi scale score was available were classified as probable cases of PTSD.

For subjects who had not been adjudicated as having service-connected PTSD, a low cutoff score of 89 on the Mississippi scale was selected, which would ensure high sensitivity at the expense of specificity. This choice was confirmed by interviewing 17 randomly chosen subjects who scored below 89, only one of whom was found to have (past) PTSD. Subjects not adjudicated as having service-connected PTSD who scored 89 or above were invited to take the SCID,

TABLE 1. Lifetime Diagnoses of PTSD According to the Mississippi Scale for Combat-Related PTSD and the SCID* for 156 Wounded Vietnam Veterans

Method of Diagnosis	Subjects With PTSD (N=63)		Subjects Without PTSD (N=93)	
	Definite	Probable	Definite	Probable
Subjects with VA rating of service-connected PTSD (N=25)				
Mississippi scale score <107		4		
Mississippi scale score ≥107	13			
No Mississippi scale score		8		
Subjects without VA rating of service-connected PTSD (N=131)				
Mississippi scale score <89				
With SCID	1		16	
Without SCID				63
Mississippi scale score ≥89				
With SCID	26		11	
Without SCID				3
Mississippi scale score <107		11		
Mississippi scale score ≥107		23		
Total	40	23	27	66

*SCID=Structured Clinical Interview for *DSM-III-R*.

which was administered by a clinical psychologist (B.A.) who had undergone training in its use. Informed consent was obtained after the procedure had been fully explained. Subjects found to meet the *DSM-III-R* criteria for PTSD on the SCID were classified as definitely having PTSD; those not meeting these criteria were classified as definitely not having PTSD. For subjects who had not been adjudicated as having service-connected PTSD and who were not interviewed, those with Mississippi scale scores of 107 or higher were classified as probably having PTSD, and those with scores below 107 were classified as probably not having PTSD.

Interviewed subjects were classified as having immediate or delayed PTSD according to whether the diagnostic criteria had been met within 6 months of combat; they were classified as having past or current PTSD according to whether the criteria were met during the preceding month. Comorbid axis I diagnoses were also classified as past or current. For subjects who were diagnosed as having PTSD but who had not been adjudicated by the VA as having service-connected PTSD, the interviewer inquired about the reason.

RESULTS

The results appear in table 1. Of the 27 subjects with diagnoses of PTSD according to the SCID, 24 (89%) had immediate and three (11%) had delayed onset; 22 (81%) had a current diagnosis of PTSD and five (19%) had only a past diagnosis of PTSD. Only two (7%) of the subjects had PTSD as their sole lifetime axis I diagnosis; the remainder had the following additional disorders: 18 (67%), alcohol dependence or abuse (five current); eight (30%), other psychoactive substance dependence or abuse (one current); 17 (63%), major depression (five current); seven (26%), panic (four current); seven (26%), social phobia (four current); six (22%), generalized anxiety; five (19%), obsessive-

compulsive disorder (five current); four (15%), simple phobia (three current); three (11%), dysthymia; five (19%), other disorders (four current).

Reasons given by the subjects with current PTSD for not having it as a service-connected disability were as follows: nine did not know about PTSD or did not know that they had it, three did not want the "hassle" of applying for benefits, three already had other service-connected psychiatric conditions, two felt they did not need compensation, one did not know how to apply, one did not want it on his record, one did not want to "mooh off the government," and two gave no reason.

DISCUSSION

Several factors dictate that the results obtained here not be considered definitive with respect to the prevalence of PTSD in Vietnam veterans. The 64% response rate was slightly lower than the 67% (2) and 75% (3) rates reported in earlier studies; the sample was restricted to a single type of injury, source of ascertainment, and geographical area; and all of the assessment measures were not administered to all of the subjects. Nevertheless, the results are of interest for at least two reasons. First, they provide a higher estimate of the prevalence of PTSD in wounded Vietnam veterans that is based on a larger sample than previously studied (2). Second, they indicate a higher proportion of current PTSD cases than previously reported (3). Several design differences may have given our method greater sensitivity to PTSD: use of instruments validated for the population under study, interview by a doctoral-level clinician experienced with the population, and use of *DSM-III-R* criteria. Our estimate of a 32% prevalence of current PTSD in wounded Vietnam veterans (which we derived from multiplying the estimated 40% lifetime prevalence of PTSD by the estimated 81% of lifetime cases still current) is very close

to the estimated 31% prevalence of current PTSD found in Vietnam veterans with high combat exposure in a major ongoing epidemiological study (7). That study also used the SCID. These findings suggest that the choice of diagnostic instrument(s) is a crucial factor in epidemiological studies of PTSD (8).

Figures supplied by the VA indicate that the approximate percentage of Vietnam veterans with service-connected PTSD is 1.5% for New Hampshire but only 0.5% for the nation. (For the Korean War and World War II, the percentages are far lower.) The approximate ratio of Vietnam veterans with service-connected PTSD to those with service-connected musculoskeletal injuries is 0.64 for New Hampshire but only 0.24 for the nation. These figures point to a rate of service-connected PTSD two to three times greater for New Hampshire than for the United States as a whole. However, even in the New Hampshire sample studied here, only 25 (40%) of the 63 definite and probable cases of PTSD had been adjudicated as having been service-connected. Even allowing for wide margins of error in the data, these numbers suggest that despite a recent active outreach effort, the majority of combat-related PTSD cases remain unidentified by the VA.

REFERENCES

1. Robins LN, Helzer JE, Croughan J, et al: National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. *Arch Gen Psychiatry* 1981; 38:381-389
2. Helzer JE, Robins LN, McEvoy L: Post-traumatic stress disorder in the general population: findings of the Epidemiologic Catchment Area survey. *N Engl J Med* 1987; 317:1630-1634
3. Centers for Disease Control Vietnam experience study: health status of Vietnam veterans, I: psychosocial characteristics. *JAMA* 1988; 259:2701-2707
4. Spitzer RL, Williams JBW: Structured Clinical Interview for DSM-III-R—Nonpatient Version (Modified for Vietnam Veterans Readjustment Study). New York, New York State Psychiatric Institute, Biometrics Research, 1987
5. Keane TM, Caddell JM, Taylor KL: Mississippi Scale for Combat-Related Posttraumatic Stress Disorder: three studies in reliability and validity. *J Consult Clin Psychol* 1988; 56:85-90
6. Atkinson RM, Henderson RG, Sparr LF, et al: Assessment of Viet Nam veterans for posttraumatic stress disorder in Veterans Administration disability claims. *Am J Psychiatry* 1982; 139: 1118-1121
7. Kulka RA, Schlenger WE, Fairbank JA, et al: National Vietnam Veterans Readjustment Study (NVVRS): Description, Current Status, and Initial PTSD Estimates. Research Triangle Park, NC, Research Triangle Institute, 1988
8. Roberts L: Study raises estimate of Vietnam war stress. *Science* 1988; 241:788

Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

PHENOMENOLOGY AND PSYCHOPATHOLOGY

Karl Jaspers: Basic Philosophical Writings, Selections, edited and translated by Edith Ehrlich, Leonard H. Ehrlich, and George B. Pepper. Athens, Ohio University Press, 1986, 556 pp., \$55.00; \$26.95 (paper).

The centenary of the birth of Karl Jaspers, psychiatrist par excellence and one of the most outstanding thinkers of our century, occurred in 1983. The anniversary, commemorated worldwide with special programs by international societies and congresses, also stimulated the preparation of this book, a compilation of writings by Jaspers along with introductory comments and guided instruction by the editors.

Within psychiatry, Jaspers is widely acknowledged as a seminal thinker, the father of phenomenology, the leading psychiatric methodologist, and a preeminent psychopathologist. But his vast contributions to our field are a mere preface to his other contributions to the general culture—his philosophy of existence and his many books and essays on truth, communications, human nature, science, politics, and religion. In these writings, his reflections and insights are wide-ranging in scope, profound in wisdom, audacious in originality, and liberating in effect. Can there ever be another psychiatrist such as this? How fortunate we are, then, to have this single volume of critical selections from the entire Jaspers corpus freshly translated and generously commented on by leading Jaspers scholars of the present day.

The book contains 74 excerpts organized systematically in seven parts. Each part and selection is preceded by an editor's guide and commentary. There is also a complete bibliography of Jaspers's books and monographs as well as writings about Jaspers. Forty percent of the book is translated for the first time, and most of the selections from previous translations have been retranslated, including an excerpt from Jaspers's *General Psychopathology*.

Rather than attempting to review this ambitious volume as a whole, I will limit my comments to a few selections that are of particular interest to psychiatrists.

First, in selection 2, the editors justify their new translation of an excerpt from *General Psychopathology* by explaining the need to capture more faithfully Jaspers's original expression, "even where more felicitous constructions would seem desirable." The new translation leads to a richer and more personal rendering of a section that seemed dispassionate and technical in the original translation. More importantly, the more philosophical idiom of this new translation convincingly demonstrates that Jaspers's mature philosophy of existence and his philosophical anthropology were already prefigured in his much earlier work as a psychiatrist. Excerpts from Jaspers's philosophical autobiography (selection 1) are also helpful in forging a link between Jaspers's begin-

ning efforts as a psychiatrist and his later philosophical wisdom.

Second, in dealing with the relationship between philosophy and science (selections 53–56), Jaspers is deeply appreciative of the astounding successes of the modern sciences. But he is also deeply concerned that widespread faith in scientific progress blurs the distinction between science and wisdom and even undermines the basic dignity and freedom of humankind. Therefore, Jaspers emphatically insists that it is necessary to comprehend the limits of scientific activity as well as its strengths. Ultimately, scientific insights are "perspectival"—although they profoundly illuminate certain fundamental aspects of reality they do so only by ignoring or even concealing other equally basic aspects.

Furthermore, the task of appreciating the limits of scientific activity is best achieved by actually doing scientific research. Such research ultimately discloses the problems that arise at the boundaries of scientific knowledge. For the investigator, awakening to these problems can both clarify the limits within which scientific activity takes place and disclose the issues of ultimate concern that are never touched by scientific activity. Jaspers's own philosophizing began with his confrontation with these limits during his scientific work as a psychopathologist.

Third, Jaspers's depiction of communication as a "loving struggle" is of major interest to psychiatrists concerned with clinical practice and with psychotherapy. He returns to the subject of communication again and again in this compilation of his writings, both as an issue for theoretical discourse (selections 8 and 43) and more personally (in selections 67 and 68, on his relationship with his mentor Max Weber; selection 70, on his relationship with his student and friend Hannah Arendt; selections 71 and 72, on his relationship with his wife Gertrud; and selection 69, on his failed communication with Martin Heidegger). Additionally, Jaspers clarifies various psychiatric debts to Max Weber, such as the important distinction between understanding and explanation and the notion of the ideal type, which Jaspers found so fruitful in his original nosology.

Other selections of special interest include Jaspers's comments on his illness (selection 73), Kierkegaard and Nietzsche (selection 6), limit situations (selection 12), and his philosophy of existence (selections 16–28). Also of value are selections from the previously untranslated *Von der Wahrheit* (selections 35–42) and selections on philosophy and politics, philosophy and history, and philosophy and religion.

To conclude, this anthology is a substantial accomplishment and a notable contribution to our culture. Any psychiatrist seriously interested in the central problems of our field—and also of our time—should purchase it. Those who are unfamiliar with the writings of Karl Jaspers will find it an excellent introduction. Readers already familiar with Jaspers the psychiatrist will learn a great deal about his broader philosophical and cultural achievements. Finally, more knowledgeable readers will value the newly translated and retranslated material included in this book and will deeply

enlarge their understanding of Jaspers's writings as a whole. Reading Jaspers is not easy, but the struggle is most definitely loving and richly rewarding.

MICHAEL ALAN SCHWARTZ, M.D.
New York, N.Y.

NEUROPSYCHIATRY

What Is Epilepsy? The Clinical and Scientific Basis of Epilepsy, edited by M.R. Trimble, F.R.C.P., F.R.C.Psych., and E.H. Reynolds, M.D., F.R.C.P., F.R.C.Psych. Edinburgh, Churchill-Livingstone (White Plains, N.Y., Longman, distributor), 1986, 344 pp., \$74.00.

This is an excellent book with something for everyone. It has clinical and theoretical relevance for both psychiatrists and neurologists. Perhaps most important for psychiatrists are the questions it raises about behavior. George Fenton begins his excellent chapter entitled "EEG, Epilepsy and Psychiatry" with the statement, "The behavioral manifestations of epilepsy span the interface between brain and mind" (p. 139). It is really the question of the relationship between the brain (electrical activity) and the mind (behavior) that is a central theme of this book and one from which the title derives. Throughout the book one is constantly confronted with questions such as, What is epilepsy? What is a seizure? What is the significance of paroxysmal EEG electrical disturbances? Why are there electroform discharges on the EEG interictally with no seizures? What is the relationship of psychopathology to epilepsy and to these EEG disturbances?

These are not new questions, as Reynolds notes in his introductory chapter. Even Hughlings Jackson noted these ambiguities, stating, "I formerly used the term 'epilepsy' generically for all excessive discharges of the cortex and their consequences . . . I now use the term 'epilepsy' for that neurosis which is often called 'genuine' or 'ordinary' epilepsy, and for that only" (p. 4). These questions are not just theoretical. Their answers have major clinical significance. If we look at specific chapters their utility is immediately apparent, specifically, the chapter by Shorvon and Reynolds on the epidemiology and temporal patterns of seizures, Gram and Dam's chapter on paroxysmal neurological disorders such as transient global amnesia and syncope, excellent chapters by Binnie on the clinical use of the EEG, and the fine chapter already noted by Fenton on the relationship of EEG to seizure disorders and particularly the clinical interpretation of EEG abnormalities in people without "classical" seizures. Trimble contributes an excellent chapter on distinguishing hysteria and epilepsy, and there is a chapter by Toone discussing the evidence for and against epilepsy's relationship with psychopathology. Horton has a very useful chapter on the pharmacology of epilepsy with anticonvulsant drugs. Other chapters have a more basic orientation and provide further potential for speculation, such as the chapter by Chadwick and Crawford on the biochemistry of seizures, a chapter by Fenwick on the electrophysiology of EEG epileptic discharges, and an interesting chapter by Max Fink comparing ECT-induced seizures to naturally occurring seizures. An updated version of Janice Stevens's excellent paper, "All That Spikes Is Not Fits," is reprinted here, and there are also chapters on kindling and the neurophysiology of excitatory transmission. In all there are 24 fine chapters and two final

general discussion sections by all the authors—"What Is Epilepsy?" and "The Borderlands of Epilepsy."

Anyone fascinated by the biological aspects of behavior will find this book of great interest. It should be in most departmental and hospital libraries. It is a companion book to two others edited by Michael Trimble, one in 1985 on the psychopharmacology of epilepsy (1) and another in 1986 edited by Trimble and Bolwig on epilepsy and psychiatry (2). It is remarkable that there is little overlap in these three books. In general, the books complement each other and together present a comprehensive and useful trilogy for psychiatrists and neurologists. They also raise the question of why there is so much more interest in epilepsy in Great Britain than there is in the United States. Although each of the books has authors from the United States, the majority are from Great Britain and Europe. Perhaps this is due to the system of medical care: are more British and European psychiatrists involved with the seriously ill in larger hospitals and therefore come more in contact with epilepsy patients or is there a longer tradition of study of the overlap area between psychiatry and neurology in Great Britain and Europe? It is evident that U.S. psychiatrists are just becoming interested and aware of the importance of these areas of overlap as theoretical models and for their practical, clinical utility in treating such entities as multiple sclerosis and stroke. It is also interesting that U.S. psychiatrists have pioneered in the use of anticonvulsant medication in psychiatric populations but again have not paid as much attention to the area of epilepsy as is probably warranted. This book should kindle our interest.

REFERENCES

1. Trimble MR (ed): *The Psychopharmacology of Epilepsy*. Chichester, John Wiley & Sons, 1985
2. Trimble MR, Bolwig TG (eds): *Aspects of Epilepsy and Psychiatry*. Chichester, John Wiley & Sons, 1986

GARY J. TUCKER, M.D.
Seattle, Wash.

Migraine: Clinical and Research Aspects, edited by J.N. Blau. Baltimore, Johns Hopkins University Press, 1988, 695 pp., \$79.50.

In some primary care settings, 20% of the patient visits are for the complaint of head pain. Therefore, all physicians should be familiar with the common headache syndromes. A subset of patients with head pain will be referred to psychiatric physicians due to psychological factors involved in the genesis of the complaint or as a reaction to disabling symptoms. This volume comprehensively reviews the diagnostic, etiological, and therapeutic issues in the migraine headache.

The book addresses the signs and symptoms of the migraine headache in adults and children. An excellent chapter by Dr. Blau discusses the course of the migraine headache from the prodroma to resolution and recovery. Dr. Blau views the migraine headache as a primary neurological disturbance with only secondary involvement of blood vessels. The varied clinical picture includes psychological symptoms and behavioral phenomena during the actual head pain, such as irritability, diminished concentration, attempts to sleep, and general behavioral withdrawal. In children, many of whom have a family history of migraine headaches, the migraine syndrome includes recurrent abdominal pain that can

concur with the head pain. Estimations of the frequency of migraine in children vary widely; it seems to occur in 3% to 4% of latency-age children.

The volume reviews the differential diagnosis of migraine headaches as distinguished from tension headaches, sinusitis, and mass lesions. The chapter on diagnostic investigations of migraine headaches explains that electroencephalography is often useful only if there is a need to exclude epileptic phenomena. The use of CT scanning is also discussed, and it is suggested that such scanning is most useful in the presence of an orbital bruit suggestive of an arterial venous malformation, a history of focal seizures, or the presence of persistent focal neurological deficits. Cluster headaches are also discussed at length. An interesting chapter deals with EEG abnormalities as well as abnormal visual evoked potentials found during the acute migraine attack.

The pharmacotherapy of migraine is carefully covered. Ergotamine and its derivatives remain the most useful agents in affecting the acute migraine attack; analgesic and anti-inflammatory agents are secondary supports. Use of α -adrenergic agents has been shown to help in the prevention of migraine phenomena, and the possible use of serotonin receptor blockers such as methysergide and calcium channel antagonists such as nifedipine is promising. An interesting chapter is devoted to the herb feverfew, which is often self-prescribed as a medication for migraine. This herb may act on prostaglandin biosynthesis or function as a calcium channel blocker and has been shown to have some therapeutic effects.

Therapeutic strategies such as explanations of the disorder and clinical problems such as excess drug use are described. Biofeedback and relaxation therapy are proposed as potential treatments, although the mechanisms of action are as yet unknown. The chapter of most interest to psychiatrists may well be "Psychological Factors in Migraine," by Harold Mersky. This excellent contribution downplays a close relationship between stress and the onset of a migraine. Furthermore, the idea of a specific personality type for migraine sufferers is discarded. Mersky concludes that amitriptyline is effective in certain patients with migraine. Whether this is due to its effect on pain or on the headache itself is not known. A recent study (1) found that depression and migraine both run in families but that depression coexisting with migraine is more likely to be a reaction to the symptoms rather than due to a genetic link between the two symptoms.

The rest of the book focuses on a wide range of etiological theories for migraine, including biochemical metabolic abnormalities, abnormalities in platelets, allergic factors, and vascular etiologies. The book critically reviews the use of β -adrenergic blocking agents in the treatment of migraine. Other topics, such as the epidemiology of migraine headaches, its genetics, and both ocular and otologic factors within the disorder are covered. The book is well produced with generous use of tables, charts, and figures.

REFERENCE

1. Merikangas KR, Risch NJ, Merikangas JR, et al: Migraine and depression: association and familial transmission. *J Psychiatr Res* 1988; 22:119-129

THOMAS N. WISE, M.D.
Falls Church, Va.

CLINICAL NEUROBIOLOGY

Dopamine Receptors: Receptor Biochemistry and Methodology, vol. 8, edited by Ian Creese and Claire M. Fraser. New York, Alan R. Liss, 1987, 264 pp., \$70.00.

Most of the other volumes in this series, although they provide some valuable texts for biochemists and physiologists, are unlikely to offer much of interest to readers of this journal. Dopamine receptors, however, have a special place in psychopharmacology and biological psychiatry. Not only are they the presumed site of action of the neuroleptic drugs, but the observation that their levels are higher in the brains of schizophrenic patients (whether or not this is related to the disease process) did much to stimulate neurochemical research in psychiatry. It would be difficult to assemble a more prestigious group of experts than the group of leading lights in dopamine receptor research who contribute the chapters of this excellent volume. It is a pleasure, too, for me as a non-American reviewer to see the international authorship of this text, which originated in the United States.

In the first chapter, one of the editors, Ian Creese, and his colleague Ellen Hess discuss the biochemical characterization of dopamine receptors in a broad introduction to their roles in CNS dopamine function and provide a short but valuable review of their pharmacology. Next, Philip Strange describes clearly the advances that he and others have made toward the (as yet) elusive goal of receptor purification and molecular characterization. Dopamine autoreceptors are discussed by Wolf and Roth in a comprehensive and accessible review touching on all aspects of the (necessarily circumstantial) pharmacological, behavioral, and electrophysiological evidence for these presynaptic mediators of dopaminergic activity. The fourth chapter, by Kohli and Goldberg, describes dopamine receptors in the periphery, particularly the distinction between receptor subtypes. Clearly, in any comprehensive review, the receptors outside the brain cannot be ignored, but this chapter appears somewhat out of place, given the CNS-oriented discussion of the rest of the text. This will matter little to those whose interests are mainly cerebral, but an attempt by the authors or editors at integrating this chapter more would have been worthwhile.

Greengard and his colleagues present their area of expertise, the functional biochemistry of protein phosphorylation, through which mechanism dopamine (and other) receptors may mediate transmitter effects on the postsynaptic cell membrane. This is followed by reviews of dopamine receptor electrophysiology, by Wang and colleagues, and autoradiographic localization, by Palacios and Pazos. The latter chapter contains several well-reproduced pictures illustrating dopamine receptor distribution in, primarily, the rat brain. The final two contributions are from Arnt, who summarizes the animal behavioral pharmacology involving dopamine receptors, and Seeman, who describes the neuropathological involvement of dopamine receptors. This brief review covers dopamine receptor changes in postmortem brains taken from patients with schizophrenia, Parkinson's disease, and Huntington's disease. It also discusses the contribution made by previous drug treatment to these results. Positron emission tomography (PET) as a means of visualizing these receptors *in vivo* is also mentioned, although unfortunately the book was published before the appearance of some of the most interesting results in this fast-moving field.

Minor criticisms include the suggestion that there is a substantial frontal cortical dopaminergic innervation in the hu-

man brain (an incorrect extrapolation from animal data) and the suggestion that tardive dyskinesia may involve increased D_2 receptor density, for which there is no supportive evidence. Nevertheless, this is a useful book with much to offer the reader. It would be a valuable addition to any medical school library, providing a comprehensive source of reference for the medical student, postgraduate researcher, or established medical scientist who wishes to understand more about the vital role of these receptors in normal and pathological brain function.

GAVIN P. REYNOLDS, PH.D.
Nottingham, England

Memory and Brain, by Larry R. Squire. New York, Oxford University Press, 1987, 294 pp., \$24.95; \$14.95 (paper).

Humans are typically complacent about their flair for higher mental functioning. Although every facet of the mind has its proponents, the ability to remember has fueled the most species-specific self-congratulation. The immediacy of experience may trick us into taking for granted our ability to perceive, reason, plan and act, and even to verbalize, but that we can remember, at will, much of what has taken place seems particularly magical. Correspondingly, it is around memory that the neuroscientific enterprise is centered, promising ultimate coherence across diverse levels of analysis, a fact that afforded Larry Squire the opportunity to write this book.

Where do memories come from? Where are they when they are not being remembered? Such obtusely formulated questions have generated a spate of biologically incoherent metaphors—stores, boxes, lexicons, pigeonholes in the head—each populated with a different subset of memoranda and bearing distinctive “addresses,” variably “legible” (to whom?) when they are “accessed” (by what?) to be retrieved.

These metaphors imply that the brain squirrels away a shrewdly selected subset of what is experienced against the day when it might usefully be remembered. How vacuous this view is becomes apparent given that the mere passage of time can be remembered. Are we to suppose that every event starts its own personal “temporal register,” which then counts indefinitely just in case the individual might sometime wonder how long it has been since it happened. Lashley was right in judging the search for the engram futile. Specific memories have never been localized to specific sets of neurons or eliminated by inactivating specific sets of neurons. In contrast, research has uncovered much neural machinery that enables remembering. Function is localized, all right, but information is not.

Departing from his generally uncritical stance, Squire refers to “Lashley’s error” (p. 67) in considering the neurons that are active when something is remembered to be widely distributed. However, in his principle of regional mass action, Lashley was exactly on the mark. Within a categorical domain, partial damage does not restrict the set of potential responses but decreases the probability of response across the full set. The experimental findings point to extensive neuronal systems predisposed to respond in specific ways, depending on the eliciting circumstances. No particular response lurks expectantly in its individualized niche.

The lesson has proved hard to learn, not only for cellular neurophysiologists, who fantasize an analogue of human memory in the adaptations of an invertebrate neuron, but also for cognitive scientists, who should know better than to

populate the brain with boxes. “The most likely site of storage is the set of particular cortical processing systems that are engaged during the perception, processing and analysis of the material being learnt” (p. 123). Although clinical neuropsychology has taught us that quite restricted areas of cortex are necessary for particular mental operations, cerebral metabolism studies suggest that quite broad territories are essential even for the most simple of tasks.

The foregoing illustrates what Squire readily concludes: that the study of memory and brain has far to go (p. 24). It has gone farthest in defining systems that facilitate particular types of remembering, such as the reexperiencing of an event as distinct from the automatizing of a response. Although he insists too much on his own pet distinction between procedural and declarative memory, his book serves a much broader purpose than the propagation of a particular doctrine. He introduces attempts to clarify memory at many different levels of analysis, from molecular to behavioral. Coordinating these levels is a task for the future. Squire proceeds from his vantage points in human and primate neuropsychology in his first attempt to render coherent the loose-knit concept of memory “neuroscience.” The reader interested in what is currently held to be important in brain-based memory research could with advantage begin with this pleasantly written introductory text.

MARCEL KINSBOURNE, M.D.
Waltham, Mass.

From Learning to Love: The Selected Papers of H.F. Harlow, edited by Clara Mears Harlow. New York, Praeger, 1986, 334 pp., \$55.00.

This book is part of the Centennial Psychology Series, which has been especially designed for courses on the history of psychology. Each volume in the series focuses on one important contributor to the behavioral sciences. The behavioral scientist being honored in this volume is Harry Harlow, an extremely well-known creative, irascible, caring, pioneering, driven psychologist whose work has dramatically affected the field of psychiatry in addition, of course, to psychology and primatology. This book was invited in 1980 and finally published 6 years later.

There may be some interest in knowing what other scientists have been honored with volumes in this series. They include Anne Anastasi (*Contributions to Differential Psychology*), John J. Atkinson (*Personality, Motivation, and Action*), Raymond B. Cattell (*Structured Personality Learning Theory*), William K. Estes (*Models of Learning, Memory, and Choice*), Hans J. Eysenck (*Personality, Genetics and Behavior*), Irving L. Janis (*Stress, Attitudes and Decisions*), David C. McClelland (*Motives, Personality, and Anxiety*), Neal Miller (*Bridges Between Laboratory and Clinic*), Brenda Milner (*Brain Function and Cognition*), O. Hobart Mowrer (*Leaves From Many Seasons*), Charles E. Osgood (*Language, Meaning, and Culture*), Julian B. Rotter (*The Development and Applications of Social Learning Theory*), Seymour B. Sarason (*Psychology and Social Action*), and Benton J. Underwood (*Studies in Learning and Memory*).

In the introductory part of the book there is a summary of the evolution of Professor Harlow’s research written by Clara Mears Harlow, his first and third wife. The basic biographical information, which by itself will be interesting for psychiatrists, is interspersed with personal anecdotes. If you

don't read any other parts of the book by all means read this section.

The remainder of the book is basically a collection of reprints of Professor Harlow's more famous papers divided into sections entitled Learning, Discussion, Motivation, Affection, and Psychopathology. The sixth section of the book is an overview that contains a previously unpublished lecture on love and aggression given by Professor Harlow to the Kittay Foundation on October 31, 1976, and a reprint of a paper on psychopathological perspectives written by Melinda Novak and Harry Harlow.

If one would like to have easy access to a collection of Harry Harlow's better-known papers, this is the book to have. There is no new information here other than the anecdotes in the beginning, but critical papers in each of the above areas are reprinted in one collection. The photographs are spectacular and liberal in number (about 140 figures, including many animal pictures), reflecting the high quality of the work of both Robert Sponholz and Bob Dodsworth. This book would never have made it without the efforts of Helen Leroy, who, in addition to Clara Mears Harlow, worked so hard to produce it.

In my view, Harry Harlow's work on attachment systems, on learning, and on motivation should be a basic part of requirements of every psychiatry residency. It forms an important part of a developmentally based psychiatry. He had a wonderful wit, a sense of humor, and a writing style that makes reading his works pleasurable as well as informative.

As this area of our field now moves in a major way to build bridges to the developmental neurosciences in new and exciting ways, Professor Harlow would be pleased. Yet, he would be able to view overly reductionistic views of how behavior and neurobiology interrelate with a certain amusement, irritation, and humor. Harry was not always fond of psychiatrists and often the feeling was reciprocated. I was one of the fortunate psychiatrists to have the opportunity (and challenge) of working with him for a time when he was productive on the interface of science and not content to do "me too" experiments. For this I will always be indebted. I urge my psychiatric colleagues to read as much of him as possible in the areas mentioned above and to incorporate more of his writings into our medical student and residency education programs, especially in child psychiatry.

WILLIAM T. MCKINNEY, M.D.
Madison, Wis.

CREATIVITY

Psychoanalytic Perspectives on Art, vol. 2, edited by Mary Mathews Gedo. Hillsdale, N.J., Analytic Press, 1987, 342 pp., \$34.50.

In the introduction to the first volume of *Psychoanalytic Perspectives on Art* (1), the editor writes that this publication "inaugurates not only a new journal but an entirely new species of art periodical. Until now," she continues, "no publication in the visual arts has addressed itself primarily to exploring the meaning of the work—its style as well as its iconography—as a reflection of its creator's inner world." Furthering this exploration, volume 2 focuses on nineteenth-century Impressionist and Post-Impressionist painting.

Complementing recent quantitative empirical diagnostic studies of depression in artists, many of the authors in this

second volume examine the role of depression in the lives and works of the artists they cover. There are no statistics to persuade the skeptics, but I found these essays a welcome addition to the literature. For example, in the essay "Monet, Madness, and Melancholy," Steven Z. Levine shows how "Monet's own discourse on madness and melancholy begins in the surviving letters of 1864, his first year of substantial artistic work." Levine suggests "a pattern of elation and depression going well back into Monet's childhood."

In the essay "Two Self-Portraits by Berthe Morisot," Beth Genné provides a careful visual analysis of these two works in the light of the artist's letters and notebooks as well as accounts of her behavior. Citing evidence that the artist experienced periods of depression, Genné perceptively reads one of these self-portraits as a reflection of Morisot's "vulnerable side—depressed and without confidence, saddened, and emotionally overwhelmed by the changes in her life." The author documents that these two self-portraits, representing contrasting aspects of the artist's personality, were created by Morisot during a period of personal crisis. Since self-portraits are uncommon in Morisot's oeuvre, this "case report" provides independent confirmation of Francis V. O'Connor's thesis, presented in the first volume of *Psychoanalytic Perspectives on Art* (1), that the frontal self-portrait marks "points of transition and crisis in the life course of its creator." O'Connor himself provides another confirmatory case report in this volume in his brief article entitled "True Grit: A Note on a Frontal Self-Portrait by Queen Victoria."

When reviewing Reinhold Heller's book *Munch: His Life and Work*, Thomas L. Sloan shows how "melancholy in its numerous guises . . . along with the personal vulnerabilities it exposes is an essential element of Munch's personality and his visual language." This book review and the companion piece by George Moraitis, together with a response by Heller, provide a stimulating interdisciplinary exchange complementing the extensive essay on "Edvard Munch: The Creative Search for Self," by Lawrence and Elaine Warick.

Regrettably, the very promising "interdisciplinary dialogue" between the psychoanalyst John Gedo and the art historian Theodore Reff on the art and life of Paul Cézanne did not turn out as intended. In the words of the editor, "this dialogue—consisting of two pairs of essays—soon derailed and turned acrimonious," painfully revealing the hazards inherent in this innovative interdisciplinary undertaking.

Other articles in this volume include "Delacroix: A Study of the Artist's Personality and Its Relation to His Art" by Jack J. Spector, "The Psychodynamics of Modernism: A Postmodernist View" by Francis V. O'Connor, "Manet's Empathy" by Joel Isaacson, "The Pathology and Health of Art: Gauguin's Self-Experience" by Donald B. Kuspit, and "Thomas Eakins and S. Weir Mitchell: Images and Cures in the Late Nineteenth Century" by Norma Lifton.

The essays in volume 2 differ markedly in scope, style, and length. They are all ambitious. They are not all successful. But taken together they have convinced me that *Psychoanalytic Perspectives on Art* is a series worth reading.

REFERENCE

1. Gedo MM: *Psychoanalytic Perspectives on Art*, vol 1. Hillsdale, NJ, Analytic Press, 1985

JOSEPH J. SCHILDKRAUT, M.D.
Boston, Mass.

The Creative Process of Psychotherapy, by Arnold Rothenberg. New York, W.W. Norton & Co., 1987, 210 pp., \$24.95.

This book attempts to understand the process of psychotherapy by comparison with the creative process. The author has had a longstanding interest in the process of creativity and, in fact, tells us in the introduction that he has developed an "interview focused on works in progress . . . with persons who by general consensus are considered to be creative." He states,

Starting the inquiry with the creative work and tracing psychological processes related to the production of that work increased the likelihood that any findings would be directly related to the creative process. I chose initially to carry out the research with literary creative persons because I knew literature fairly well and also because I suspected that factors in verbal creativity might be directly applicable to the verbal interaction of psychotherapy. (p. xiv)

The only other description of this research comes from the statement that he interviewed more than 75 creative persons for "a total of more than 1800 hours." On the other side—that is, psychotherapy—he reports that he continued to practice psychotherapy and "observed the therapeutic work of my colleagues and supervisees."

The contents of the book focus on the common elements and interactions in the two fields—the homospatial process (i.e., actively conceiving two or more discrete entities occupying the same space), the Janusian process (actively conceiving two or more opposites simultaneously), and the articulation process (the process by which the patient must actively adopt a new pattern of behavior). These and other types of thinking are linked to the elements of the classical models of psychotherapy, including empathy, insight, countertransference, and paradox. Throughout the book Dr. Rothenberg selectively and extensively provides examples from poets, playwrights, and artists as well as from family and individual therapists.

The author's intent is to "show that psychotherapy shares many constituents with the creative processes in other fields such as the arts and sciences" and to help therapists become more creative (and, by implication, better therapists). Dr. Rothenberg is more successful with the former aim. Regarding the latter he states,

As I have suggested throughout, creative activity is necessary to move the practice of psychotherapy into more efficient and effective directions. Moreover, the capacity to engage in such creative activity does not appear to be inborn, for either therapists or patients. The processes I have discussed have all already been employed and further learning is feasible. Although all have operated in outstanding and often dazzling accomplishments in other creative fields, their increased application to psychotherapy will produce less tangible but no less important individual results. (p. 180)

In my judgment, as he implies, this hope remains to be demonstrated. In part this is because, as of now, the field of psychotherapy research has not yet demonstrated that what is effective is creative or that what is creative is effective.

This book will be of interest to those whose primary interest is in the study of classical psychotherapy. The writing

is often turgid and, in addition, it seems somewhat dated, as in the statement,

In schizophrenia, as in other types of narcissistic disorders, there invariably is a preoccupation with perfection and, because of primitive fusions and projective identifications, there is an inability to accept any lack of perfection in the therapist. (p. 166)

IRA D. GLICK, M.D.
New York, N.Y.

The Life of My Choice, by Wilfred Thesiger. New York, W.W. Norton & Co., 1988, 459 pp., \$25.00.

The call of adventure has powerful sway over some men. Wilfred Thesiger has been drawn to some of earth's least hospitable extremes by this unorthodox obsession. For more than half a century the author of *The Life of My Choice* pursued a nomadic existence through the most primitive regions of desert Africa. Thesiger, the son of a British diplomat, recounts his wanderings in vivid recollections, but the viewpoint is a bit unusual. The reader has an opportunity to share the author's empathy with elemental social orders, but the main theme is Thesiger's admiration for the unexpected generosity, intense interpersonal bonding, and raucous ritualism of isolated nomadic societies.

A central pillar of the author's character is fin de siècle British colonialism. He was born in 1910 in Addis Ababa, Abyssinia (later Ethiopia), where his father—descendant of a distinguished lineage of military and public patrons—was the highest ranking British minister. During this period Abyssinia was gripped by brutal civil warfare, and Thesiger's early childhood memories were heavily embossed by the pagantry of primitive warrior armies. He writes, "That day implanted in me a lifelong craving for barbaric splendor, for savagery and colour and the throb of drums, and . . . that it gave me a lasting veneration for long-established custom and ritual, from which would derive later deep-seated resentment of Western innovations in other lands, and a distaste for the drab uniformity of the modern world."

His father died in 1920, after the family had returned to England, leaving Thesiger in an alien world. The youthful expatriate found the patrician English environment incongruent with his experiences of untamed Africa. He had barely heard of cricket and was painfully rejected by his schoolmates. This early estrangement amplified itself in later life as a need for dependable and loyal relationships. He accurately charts this connection when he writes, "I have, however, been mostly content when I have established a close friendship with individuals . . . Strangely, I have found this comradeship most easily among races other than my own."

After boarding school in Sussex, he attended Eton and then Magdalen College, Oxford. There he studied history and excelled in boxing, favoring the individual, primal challenge over conventional team sports. His studies were colored by a romantic version of history rather than the industrial and economic emphases of the history curriculum. This is understandable, since as an impressionable young boy he had traveled through lands ruled by warriors and had witnessed feudal rituals that few, if any, outsiders had ever seen. Enthralled by the splendor of history, he relates, "I could visualize the first restless stirring among the tribes on the steppes of Central Asia, then the terrifying eruption of

hordes of unknown people: lurching, creaking wagons, unkempt women and children, squat, slit-eyed men in padded garments, innumerable horses, felt tents, troops of mounted archers ever on the move. I saw them as a people honed by the sun and the wind to essential flesh and bone, accustomed since childhood to hardship, possessed of extraordinary mobility and genius for war."

He was invited in 1930 to Addis Ababa for the coronation of Haile Selassie, heir to the throne of Solomon and Sheba. Having known Haile Selassie as a childhood family friend, Thesiger venerated this African leader—to whom this book is dedicated—and nurtured a lifelong devotion to the destiny of Abyssinia. With Haile Selassie's approbation he organized a hazardous journey into the Danakil tribal lands of northern Abyssinia to explore and chart the unmapped Awash River. Previous expeditions had been annihilated, but Thesiger found the risk in this faraway, unrelenting land wholly satisfying. He commented, "As I looked round the clearing at the ranks of squatting warriors and the small isolated group of my own men, I knew that this moonlight meeting in unknown Africa with a savage potentate who hated Europeans was the realization of my boyhood dreams."

World War II erupted while Thesiger was working as a civil servant on the Sudan frontier. He immediately volunteered to fight with the irregular British forces. Assigned to Wingate—who would later achieve renown in Burma—he received a Distinguished Service Order while campaigning against the Italians in Abyssinia. Subsequently, he served with David Stirling's extraordinary commando force and participated in long-range raids against Erwin Rommel's Afrika Korps in the vast Libyan Desert.

After the war, Thesiger judged the exploration of Rub al Khali, the Empty Quarter of Arabia, the most important challenge of his life. Surrounded by a no man's land of warring tribes, this enormous inviolate tract of desert had previously been regarded as inaccessible (at that time no airplane had successfully transnavigated the forbidding expanse). Thesiger spent 5 years in the Empty Quarter accompanied by the Bedouin, eventually concluding that the hardships would have been pointless penance if not for their straightforward companionship. He grew to admire the struggle between man and the harsh, unforgiving exigencies of nature: "I knew I would not match them in physical endurance but, with my family background, Eton, Oxford, the Sudan Political Service, I did, perhaps, think I would match them in civilized behaviour."

Thesiger's travels and adventures rank in the legendary traditions of Sir Richard Burton and T.E. Lawrence. He has been awarded, among many other accolades, the Founder's Medal of the Royal Geographical Society, Honorary Fellow of the British Academy, and Honorary Fellow of Magdalen College, Oxford. Two of his earlier books, *Arabian Sands* (1) and *The Marsh Arabs* (2), describe Thesiger's exploits afoot in Arabia and Iran in the same understated style found here. As a man serious about geography, he illustrates *The Life of My Choice* with carefully detailed maps. However, post-World-War-II nationalism has erased many of the nostalgic old names. Today there is no Abyssinia, French Equatorial Africa, Belgian Congo, or Tanganyika. (An armchair explorer should be well-armed with current maps of the Horn of Africa to appreciate the true diversity of Thesiger's wanderings.)

Underlying the retelling of these arduous journeys on foot and camelback is his obvious love for a remote life, greatly dependent on the individual worth of loyal companions. He trekked in the traditions of the past and, despite the preva-

lent imperialist fervor of the era, never attempted to change the people or the lands. He desired only to arrive before the intrusion of our ever-encroaching technological age. Although he spent his life in both worlds, he appreciated—far in advance of some current understanding—that the lessons learned in each are not directly translatable to the other.

A psychiatrist will recognize the author's limitations in exploring motives and emotions. He is at his best in action dramas, battle scenes, ritualizations, and primal lion hunts. What remains an enigma are the topics not addressed: Thesiger reveals no desultory vices or great interest in sex; women are scarcely mentioned. The people he admires do not seek the trappings of Western civilization or the pursuit of position, status, salary, or pension. *The Life of My Choice* is a study of purposeful single-mindedness at the expense of typical human temptations. As with many esteemed individuals, he has tailored his own narcissistic endeavors into socially sanctioned enterprises with great talent.

The strength of Thesiger's story is his introduction of the reader to people and lands that do not comfortably fit our perceptions of the twentieth century. Cast against a vanishing background of desert tribes, empty spaces, and formidable expeditions over parched escarpments where even camels collapse and die, Thesiger has found something of value in the ancient virtues of courage, endurance, and loyalty. He appreciates these convictions in remote, nomadic societies, and he decries their decline in our Western civilization.

Today, at age 78, Wilfred Thesiger resides in a Chelsea flat in London, where he reminisces with Oxford friends and enjoys membership in The Travellers, a renowned adventurers' club. Each year he ventures back to the Great Rift Valley and lives for several months in a mud-walled hut among the Samburu tribe of northern Kenya.

REFERENCES

1. Thesiger W: *Arabian Sands* (1959). New York, Viking Press, 1984
2. Thesiger W: *The Marsh Arabs*. New York, EP Dutton, 1964

CDR. JOHN R. CUSACK, MC USN
Charleston, S.C.

TEXTBOOKS

The New Harvard Guide to Psychiatry, edited by Armand M. Nicholi, Jr., M.D. Cambridge, Harvard University Press, 1988, 827 pp., \$45.00.

During the past 10 years since *The Harvard Guide to Modern Psychiatry* (1), the well-known predecessor to this book, was published, the information explosion has made it necessary for an editor of any textbook of psychiatry, other than an encyclopedia, to select critically the material to be presented and even then to prune it. The editor of this new Harvard guide, Armand Nicholi, has succeeded at this task. He has provided an informative and clinically meaningful textbook of psychiatry in less than 900 pages. It has an attractive format and is in print that is large enough to read.

The New Harvard Guide to Psychiatry is organized coherently. It consists of six major parts: Examination and Evaluation, Brain and Behavior, Psychopathology, Principles of Treatment and Management, Special Populations, and Psychiatry and Society. The 36 chapters are written by au-

thorities in their respective fields. Each chapter covers its topic in about 20 pages and, with only a few exceptions, each is well written.

This volume has many strengths, including the quality of the information presented, the format, and the clarity of the writing. Importantly, it has clinical utility. In my opinion, the emphasis given to psychopathology is especially worthwhile. Section three, Psychopathology, includes chapters on personality, defense mechanisms, and basic psychopathology that merit attention. Also, the chapters in part five, Special Populations—children, adolescents, the elderly, the mentally retarded, the substance dependent, the chronically mentally ill, and those who are confronting death—are succinct and will increase students', residents', and clinicians' understanding of these special groups. In part six, Alan Stone's chapter "Psychiatry and the Law" is informative and interesting and will be valued by clinicians who, increasingly, are confronted by forensic issues.

The weakness of the volume, which, generally, is a weakness of any multiauthored textbook, is that there is some variability in depth of information and clarity of writing from chapter to chapter. In addition, this excellent textbook would have benefited considerably by having a chapter devoted to the family; in fact, I was surprised to find that the family is a somewhat neglected topic.

I recommend *The New Harvard Guide to Psychiatry*. It will be useful to students and residents as well as to psychiatrists in clinical settings. In addition, it should be especially helpful to mental health professionals who are not psychiatrists inasmuch as it describes effectively what psychiatry is and how a psychiatrist can practice, teach, and study.

REFERENCE

1. Nicholi AM Jr: *The Harvard Guide to Modern Psychiatry*. Cambridge, Belknap Press (Harvard University Press), 1978

JOHN J. SCHWAB, M.D.
Louisville, Ky.

Behavioral Counseling in Medicine: Strategies for Modifying At-Risk Behavior, by Michael L. Russell, Ph.D. New York, Oxford University Press, 1986, 322 pp., \$29.95.

This book is designed to provide a comprehensive background of the counseling process with detailed instructions in techniques of interviewing, identifying problem behaviors, selecting goals, and developing behavioral profiles. The theoretical principles of stimulus control, shaping, behavior substitution, positive and negative reinforcement, and punishment are explained at length. Since this work is targeted for clinicians of all kinds, these preliminary considerations are quite appropriate, although this strictly phenomenological approach may be a little strange to those with strictly medical training.

The later chapters of the book deal with techniques of maintaining behavioral change and specific counseling areas. The chapter on nonadherence to medication regimens is particularly good and should be required reading for all prescribing clinicians. Such common problem areas as nonadherence to diets, noncompliance with physical activity instructions, and not stopping smoking are dealt with in detail with instructions for counseling provided in a stepwise, rather "cookbook" manner. The diet and weight control

chapters are particularly comprehensive and provide insights, case examples, and counseling strategies that should be helpful to anyone involved in patient management.

It is currently fashionable to discuss "stress," and this book is no exception. However, the chapter "Stress Management" contains little that is new. Desensitization by reciprocal inhibition, relaxation training, and stimulus avoidance are the main techniques discussed. Finally, quite good guidelines for referral for psychotherapy are presented.

Overall this book is of limited practical value to the clinical psychiatrist. It is, however, educational, instructive, and well planned and provides us with insights as to what is actually going on when patients receive counseling during visits to their family physician or internist.

DAVID TINGLE, M.D., M.P.H.
Gainesville, Fla.

The Care of Patients: Perspectives and Practices, revised ed., by Mack Lipkin, M.D. New Haven, Conn., Yale University Press, 1987, 235 pp., \$32.50; \$11.95 (paper).

The reader of this thoughtful and scholarly book will probably enjoy it and will readily perceive that it is written by an experienced clinician who cares for his patients and his profession. My reactions to the book were extremely positive as I considered its value to medical students and young physicians in the attitudes it shares about illness and the physician-patient relationship and in its teaching ways of assessing patients and planning treatment. I was disappointed, however, as a psychiatrist, by the small value Lipkin places on psychiatric interventions, whether psychotherapeutic or psychopharmacological.

Lipkin's presentations of the patient as a person, the roles and responsibilities of the physician, the physician-patient relationship, and the art of medicine are superb. He conveys the crucial importance of physicians' caring for their patients and using well-developed interactional skills in exploring symptoms, concerns, and beliefs and in explaining, educating, and "psychotherapy." Observing that most physicians seem to assess their patients primarily to establish a physical diagnosis, he presents a comprehensive system of assessment that includes the etiological, the anatomic, the pathophysiological, and the functional (including physical, psychological, and social facets). He also advocates a treatment plan that always includes physical, psychological, and environmental interventions and emphasizes that a careful estimate of the patient's prognosis must be made before a rational treatment plan can be developed.

Excellent sections of the book deal with ways of thinking about disease and illness, disease etiology (including a repudiation of the "organic versus functional" dichotomy), the truth-telling and life-prolonging roles of the physician caring for patients with life-threatening illnesses, the interpretation of laboratory data, and the use of consultants. Lipkin's reflections on the history of medicine in respect to etiology or causation of illness and ever-changing methods of treatment are both interesting and illuminating. Although the emphasis of the book is on patient care, his thoughts on observational bias and on decisions about which data to collect should be of value to young investigators.

Most psychiatrist readers will be disappointed or will perceive the book as flawed because of what it says and what it does not say about psychiatry, psychotherapy, and psychotherapeutic drugs. Although Lipkin sets forth "psycho-

therapy" as one means through which physicians can care for their patients, he does little more than list suggestion (placebo), reassurance, ventilation, persuasion, and relaxation as possible therapeutic interventions. He displays a clear-cut bias against psychoanalysis, devoting several pages to undercutting remarks. Moreover, his bias against all forms of formal psychotherapy (with the possible exception of behavior therapy) is quite perceptible. Strangely, he also presents all psychotherapeutic drugs in a negative light, not distinguishing between tranquilizers and antidepressants.

Yet the power of Lipkin's concern for the patient's indi-

viduality and his logical thoughts about the diagnostic process and treatment planning are so needed by medical students and residents that I wish this book were a required text for all introduction to clinical medicine courses. Failing that, I wish it were required reading in the first week of all junior psychiatry clerkships. Short sections of it would be very helpful in courses in medical communication skills and in physical diagnosis.

ALICE DEAN KITCHEN, M.D.
St. Louis, Mo.

Reprints of Book Forum reviews are not available.

ABPN Part I Written Application Deadline

Applications for the 1990 part I (written) examination are currently being accepted by the American Board of Psychiatry and Neurology (ABPN). All applications must be received in the Board's office *no later than September 1, 1989. No application requests will be taken after August 30, 1989.* The date for the 1990 part I examination is April 3, 1990. For application materials please contact Stephen C. Scheiber, M.D., Executive Secretary, 500 Lake Cook Road, Suite 335, Deerfield, Illinois 60015.

Letters to the Editor

Violent Crime Possibly Associated With Anabolic Steroid Use

SIR: Harrison G. Pope, Jr., M.D., and David L. Katz, M.D. (1) recently drew attention to a high frequency of affective and psychotic symptoms in bodybuilders and football players who have been taking anabolic steroids to increase muscle size and strength. In their study, gymnasiums in the United States were contacted with an offer of small payments for confidential interviews with users of steroids. Of the 41 subjects located, 15 reported major psychiatric symptoms. The subjects routinely used doses 10–100 times higher than those reported in medical studies. We report a case in which the use of anabolic steroids in this fashion may have been associated with the committing of a serious violent crime.

Mr. A was a 32-year-old Caucasian amateur bodybuilder who had been convicted of the second-degree murder of his common-law wife. Three months before the crime, he had started taking anabolic steroids on the advice of friends at the gym, who had reassured him that there were no adverse effects. By his recollection, he had been taking "Dianabol," 6 tablets a day orally, and half a vial of "Deca" by intramuscular injection once a week. (Dianabol is a methandrostenolone not formally available in Canada; six 5-mg tablets a day constitute a dose at least six times higher than advised. "Deca" is assumed to be Deca-Durabolin, or nandrolone decanoate; half a vial would be either 50 mg or 100 mg, depending on the preparation used, and the recommended interval between injections is 3–4 weeks.) About 4 weeks before the crime, Mr. A had become "hyper": irritable, quarreling noisily, sleepless, and consuming increasing amounts of alcohol. On the night of the crime, both he and his wife had been drinking heavily. As she talked about her infidelities, he "snapped." She was severely beaten and died of a subdural hematoma. There had been episodes of casual drunken violence before, but never like this. Testimony was introduced at the trial that he had become a changed man before his crime, but the use of steroids was not mentioned. At the time of the crime, Mr. A's severe abdominal pains were under medical investigation, but his physician did not know about the steroids. Mr. A had no significant previous psychiatric history and no previous criminal history. Results of a mental state examination 6 months after the crime were unremarkable.

The fact that consumption of alcohol was involved in the crime illustrates the difficulty of drawing firm conclusions from isolated case reports. The reported personality changes, including increased alcohol consumption, came after the use of steroids, and the degree of violence on this occasion was markedly different from that in previous episodes in which alcohol had also been implicated.

It is important that the possible dangers of steroid use be stressed to athletes involved in strength and endurance

events, and physicians should be aware that these individuals may conceal steroid use.

REFERENCE

1. Pope HG Jr, Katz DL: Affective and psychotic symptoms associated with anabolic steroid use. *Am J Psychiatry* 1988; 145: 487–490

G.N. CONACHER, M.B., CH.B., M.R.C.PSYCH.
D.G. WORKMAN, M.D.
Kingston, Ont., Canada

Anxiety in a Patient During an Unconsciously Experienced Earth Tremor

SIR: I should like to report the following case.

Ms. A was a 44-year-old married woman with a history of agoraphobia with panic attacks whose condition had been monitored for the past 7 years. Her symptoms were held in check by psychotherapy and the use of clonazepam, 2.5 mg/day, and amitriptyline, 50 mg/day. One day, when the patient was at home washing her face, she suddenly and unexpectedly experienced symptoms she had not had for years: anxiety, palpitations, and depersonalization, which she described as the feeling of "not being in my body." She feared falling and crawled on her hands and knees into bed. To her utter disbelief, she felt much better minutes later; this was in distinct contrast with her past history.

Later that day a friend with a history of agoraphobia who had no knowledge of what had transpired telephoned her to report that she had had a full-blown panic attack, the worst in years. The patient found this to be a "strange coincidence." Both women had experienced the return of old symptoms at the same time that day, and both had promptly recovered. In the course of that evening, the patient learned that an earth tremor had taken place at the exact time of her and her friend's panic attacks. She felt immense relief because she was able to attribute the return of her symptoms to an external cause and did not have to fear the return of her ailment. The earthquake registered 6 on the Richter scale, had its epicenter in the province of Quebec, and was felt all the way to Ontario, Michigan, and New York State.

This case suggests the possibility that some patients with histories of agoraphobia with panic attacks are highly sensitive to gravitational changes. A slight earth tremor, even though consciously unknown to this patient, was registered in her body and experienced as anxiety. Vestibular disturbances can evoke anxiety; a relationship between vertigo and agoraphobia was first proposed almost a century ago (1), and more recently it has been claimed that most "phobias" are rooted in inner-ear disturbances (2). A pilot study done

by Jacob et al. (3) found abnormal vestibular responses in a group of patients with histories of panic attack. Was the sequence of events reported here the result of a vestibular dysfunction in the patient, or was it, rather, a nonsignificant chance observation?

REFERENCES

1. Freud S: On the grounds for detaching a particular syndrome from neurasthenia under the description "anxiety neurosis" (1895), in *Complete Psychological Works*, standard ed, vol 3. London, Hogarth Press, 1962
2. Levinson HN: *Phobia Free*. New York, M Evans, 1986
3. Jacob RG, Møller MB, Turner SM, et al: Otoneurological examination in panic disorder and agoraphobia with panic attacks: a pilot study. *Am J Psychiatry* 1985; 142:715-720

DANIEL TRAUB-WERNER, M.D., F.R.C.P.(C)
Toronto, Ont., Canada

Fluoxetine Treatment of a Depressed Patient Susceptible to Malignant Hyperthermia

SIR: The pharmacologic treatment of major depressive disorder in a patient susceptible to malignant hyperthermia presents a difficult challenge for the clinician. Malignant hyperthermia, a rare familial hypercatabolic reaction associated with certain anesthetic agents (1), has also been reported in association with the use of many other medications, including tricyclic antidepressants, monoamine oxidase inhibitors, haloperidol, atropine, sympathomimetics, and quinidine analogues (1, 2). An individual's susceptibility to malignant hyperthermia is determined by demonstrating increased contraction of a skeletal muscle biopsy specimen in the presence of caffeine and/or halothane.

One acknowledged use of the newer antidepressants is in treating certain patients who experience unfavorable side effects with the older agents. In the following case report, fluoxetine hydrochloride, an antidepressant with specific serotonin uptake inhibition that is chemically unrelated to other antidepressants (3), was used safely and effectively to treat a depressed adolescent who was susceptible to malignant hyperthermia.

Anne, a 15-year-old white adolescent girl with biopsy-proven susceptibility to malignant hyperthermia, came to the inpatient unit with a several-month history of depressed mood, refusal to go to school, anorexia with weight loss, sleep disturbance, and self-destructive behavior. She had been treated for several years with phenytoin, 240 mg/day, which at therapeutic blood levels had stabilized her partial complex seizure disorder associated with a left temporal EEG abnormality. Her initial score on the Childhood Depression Inventory (4) before treatment was 20.

Because of the patient's susceptibility to malignant hyperthermia and her family history of at least one death related to malignant hyperthermia, the use of traditional antidepressants was felt to represent a severe risk. Therefore, after both the legal guardian and the patient gave informed consent, a trial of fluoxetine hydrochloride was instituted at a dose of 20 mg every other morning. There was no evidence of tachycardia, cardiac arrhythmia, hyperventilation, fever, skeletal muscle spasm or stiffness, cyanosis, or unstable blood pressure, which would have

suggested that a malignant hyperthermia event had been induced by the fluoxetine. After 1 week, the dose was raised to 20 mg/day and was maintained at that level. Clinically, the patient's mood improved, with notably decreased irritability and elimination of her suicidal ideation. Her scores on the Childhood Depression Inventory were 11, 8, 5, and 10 after weeks 1, 2, 3, and 7 of treatment, respectively. After week 2 of treatment with fluoxetine, she was thought to have improved enough to be discharged from the hospital and have only weekly outpatient visits. The beneficial effects on her mood were maintained throughout a 4-month follow-up, during which there was no evidence of malignant hyperthermia episodes or any other medication-related side effect.

Despite a recent case report of the safe use of tricyclics in a patient susceptible to malignant hyperthermia (5), the life-threatening consequences of triggering malignant hyperthermia reactions dictate caution. Although a single case report cannot provide definitive conclusions, our experience with this patient suggests that fluoxetine may be a safe and effective alternative antidepressant for individuals susceptible to malignant hyperthermia.

REFERENCES

1. Tomarken JL, Britt BA: Malignant hyperthermia. *Ann Emerg Med* 1987; 16:1253-1265
2. Gronert GA: Malignant hyperthermia. *Anesthesiology* 1980; 53:395-423
3. Fluoxetine: an antidepressant with specific serotonin uptake inhibition. *Int Drug Therapy Newsletter* 1988; 23:6-11
4. Kovacs M: Rating scales to assess depression in school-aged children. *Acta Paedopsychiatr (Basel)* 1981; 46:305-315
5. Richter MA, Joffe RT: Use of tricyclic antidepressants in a patient with malignant hyperthermia (letter). *Am J Psychiatry* 1987; 144:526

ROGER C. BURKET, M.D.
JON D. HODGIN, M.D.
Gainesville, Fla.

Arm Cutting and Glucose Level in Depression

SIR: Cutting of the forearm is a common self-injurious behavior among depressed adolescents. In normal individuals, such trauma results in hyperglycemia due to catecholamines and other hormones released during stress (1, 2). We were surprised, therefore, by the following case.

Jane was a 13-year-old postpubescent girl with psychotic depression. Her blood glucose level had dropped from 109 to 90 mg/dl 1 minute after she cut herself on the forearm during outpatient phlebotomy. Ten minutes later, her blood glucose had rebounded to 120 mg/dl. We decided to see if this effect could be reproduced in her depressed and euthymic adult relatives.

Informed consent was obtained from the adolescent's parents and aunt: a 47-year-old professional man who satisfied *DSM-III* criteria for current type II bipolar disorder, his 47-year-old wife who satisfied *DSM-III* criteria for current major atypical depression, and the latter's sister, a normal 44-year-old professional woman. The basal blood glucose level for each was within the normal reference range.

An initial specimen of peripheral venous blood was obtained from each person 4 hours after a meal and placed in a tube containing acid citrate dextrose. Each person then received a very superficial 1-cm incision on the forearm made with a number 15 surgical blade. In order to mimic self-cutting behavior, there was no preparation of the skin, nor was preparation necessary in the opinion of the Board-certified dermatologist who made the incisions. Postincision blood specimens were obtained at various intervals of time for up to 18 minutes. Blood glucose was measured, by an enzymatic method using a spectrophotometer, immediately after the blood specimens were obtained.

Blood glucose levels dropped for 1–5 minutes after the incisions in the two depressed adults: from 107 to 89 mg/dl in 1 minute in the man and from 116 to 98 mg/dl in 5 minutes in the woman. As in the case of the female adolescent, glucose levels then rebounded to be slightly higher than baseline, rising from 89 to 120 mg/dl in 9 minutes in the man and from 98 to 118 mg/dl in 11 minutes in the woman. The blood glucose level in the normal woman, by contrast, rose from 90 to 142 mg/dl in less than 1 minute and maintained that level over the next 10 minutes.

Hyperglycemia is the normal response to trauma. Bessey et al. (1) simulated the insulin resistance characteristic of post-traumatic metabolism by infusing nine healthy volunteers with cortisol, glucagon, and epinephrine. Brooks et al. (2) demonstrated posttraumatic insulin resistance by measuring decreased glucose uptake in the forearm of five patients with multiple trauma and comparing it with that of 21 healthy control subjects. We now report that cutting of the forearm initially produced the opposite effect in three depressive individuals, and the rebound was attenuated compared to the postincision hyperglycemia in a normal control subject. Several studies (3–5) have suggested that insulin-resistant hyperglycemia is characteristic of major depressive disorders. Thus, arm-cutting behavior in depressed adolescents may serve paradoxically to ameliorate insulin resistance associated with their mood disorders.

REFERENCES

1. Bessey PQ, Aoki TT, Wilmore DW: Fuel utilization following injury: relationship to hormonal environment. *J Surg Res* 1985; 38:484–493
2. Brooks DC, Bessey PQ, Black PR, et al: Post-traumatic insulin resistance in uninjured forearm tissue. *J Surg Res* 1984; 37: 100–107
3. Muller PS, Heninger GR, McDonald RK: Intravenous glucose tolerance test in depression. *Arch Gen Psychiatry* 1968; 21: 470–477
4. Sachar EJ, Finkelstein J, Hellman L: Growth hormone responses in depressive illness, 1: response to insulin tolerance test. *Arch Gen Psychiatry* 1971; 25:263–269
5. Winokur A, Maislin G, Phillips JL, et al: Insulin resistance after oral glucose tolerance testing in patients with major depression. *Am J Psychiatry* 1988; 145:325–330

ALLEN D. ALLEN, PH.D.
Northridge, Calif.
FERRIS N. PITTS, JR., M.D.
ROBERT E. ALLEN, M.D.
Pasadena, Calif.

Menstrual Cycle Phase-Related Appetite Dysregulation

SIR: Birgitta Both-Orthman and associates (1) very rightly pointed out that appetite disturbances associated with premenstrual syndrome (PMS) have received scant attention. However, we have noticed some major limitations in their otherwise sound and interesting study. The authors focused only on increase in appetite in their study. Moreover, they did not differentiate increase in appetite from craving for specific foods. Although craving for specific food items is an interesting observation, women with premenstrual syndrome may report increased, decreased, or normal appetite. In our sample of 12 women who met the *DSM-III-R* criteria for late luteal phase dysphoric disorder, increase in appetite was reported by five women, decrease in appetite by three, no change by one, and, interestingly, an irregular appetite (increased as well as decreased) by three women. Craving for specific foods was reported by these women irrespective of increase or decrease in appetite.

We related these appetite changes to the subjects' mood states by using the Premenstrual Assessment Form for Positive Emotions (P. Chandra and S.K. Chaturvedi, unpublished paper, 1988). On studying the relationship between appetite changes and positive emotions (happiness, joy, and well-being), we found that mean happiness scores increased proportionately and significantly ($p < 0.01$) with mean scores for increase in appetite. Similarly, decrease in appetite was directly related to sadness and dysphoria ($p < 0.05$), contrary to the observations of Ms. Both-Orthman and colleagues, who reported a significant relationship between dysphoria and increase in appetite.

Although their study as well as ours confirmed appetite dysregulation during the premenstrual phase, the nature of the association reported by Ms. Both-Orthman and associates appears artifactual. Researchers tend to draw wrong conclusions and make spurious inferences because they overlook an important variable in their study. For instance, it would be worthwhile to examine the correlations between decreased appetite and sadness or dysphoria as well as between increased appetite and positive emotions in the sample studied by Ms. Both-Orthman and her associates. Premenstrual alterations in mood or appetite are quite variable and perhaps biphasic (2). Like different moods (2), different changes in appetite probably coexist during the premenstrual phase in the same individual.

REFERENCES

1. Both-Orthman B, Rubinow DR, Hoban MC, et al: Menstrual cycle phase-related changes in appetite in patients with premenstrual syndrome and in control subjects. *Am J Psychiatry* 1988; 145:628–631
2. Ablan JP, Haskett RF, Rose RM: The premenstrual syndrome. *Psychiatr Clin North Am* 1980; 3:327–347

S.K. CHATURVEDI, M.D.
Manchester, England
PRABHA S. CHANDRA, M.D.
Bangalore, India

Correlates of Duration of Panic and/or Phobic Avoidance

SIR: In a secondary analysis of a previous study (1), we sought to identify important characteristics or consequences that were correlated with the duration of panic and/or pho-

bic anxiety. Although the original study used only subjects with full-blown panic, this analysis included those with limited symptom attacks as well. With 83 subjects having panic attacks and 32 demonstrating some phobic anxiety, the powers for detecting a large ($r \geq 0.50$) or medium ($r = 0.30$) effect would be 99% and 88%, respectively; for those with panic and 91% and 52%, respectively, for those with phobic anxiety (2). The dependent variables included measures of panic frequency and severity (four variables), presentation to the health care system for panic (seven variables), depression (one variable), stages in agoraphobia development (three variables), severity and pervasiveness of phobic anxiety (three variables), and lag time between onsets of panic and phobic anxiety (three variables). Correlates with durations of phobic anxiety and anticipatory anxiety were sought for all of the subjects with phobic anxiety and for those with panic attacks as a subgroup.

None of the measures of panic frequency or severity correlated with any of the durations. None of the presentation-for-panic variables correlated with duration of either panic or anticipatory anxiety. Duration of phobic anxiety was correlated with presentation to the emergency room ($r = 0.63$, $p \leq 0.025$), presentation to paramedics ($r = 0.65$, $p \leq 0.025$), and urgency of presentation ($r = 0.51$, $p \leq 0.05$). None of the durations was associated with depression, stages in agoraphobia, or severity/pervasiveness of phobic anxiety. The lag times between onset of panic and either phobic anxiety ($r = 0.71$, $p \leq 0.05$) or anticipatory anxiety ($r = 0.80$, $p \leq 0.05$) were significantly related to panic duration. As expected, the duration of phobic anxiety was significantly correlated with the durations of panic ($r = 0.57$, $p \leq 0.05$) and anticipatory anxiety ($r = 1.0$, $p \leq 0.001$), although the latter two were not associated.

Of the 63 possible correlations between the three duration variables and the 21 dependent variables, only five were significant at ≤ 0.05 . These may indeed have been due to chance alone. If not, what are these significant correlations telling us? In general, durations of panic, phobic anxiety, and anticipatory anxiety are not related to panic characteristics or severity, development or severity of phobic anxiety, or depression. The association between panic duration and lag times may indicate that those most likely to develop phobic anxiety secondary to panic attacks are particularly sensitive to these attacks. Hence, if a panic sufferer is likely to develop phobic anxiety, he or she will do it early in the course of panic disorder. The relationship of presentation for panic and duration of phobic anxiety may indicate that agoraphobic persons tend not to consult their physicians for panic attacks but instead suffer at home until a particular attack causes them extreme concern. They then overreact and either call the paramedics or go to the emergency room. Thus, the longer the duration of phobic anxiety, the more likely patients are to present in this manner.

REFERENCES

1. Katerndahl DA, Gabel LL, Monk JS: Comparative symptomatology of phobic and nonphobic panic attacks. *Family Practice Research J* 1986; 6:106-113
2. Cohen J: *Statistical Power Analysis for the Behavioral Sciences*, revised ed. New York, Academic Press, 1977

DAVID A. KATERNDAHL, M.D.
San Antonio, Tex.

Asking Patients About Symptoms of Multiple Personality Disorder

SIR: In view of the fact that the standard psychiatric history and mental status examination (1) does not include questions for eliciting symptoms of multiple personality disorder (2), and considering that in the typical case, the multiple personalities themselves have a camouflaged presentation (3), the assumption of most psychiatrists that they have no such patients either under their care or in their studies is unfounded. How can we know whether we are seeing no, few, or many cases of multiple personality if we are not even screening for, let alone evaluating for, this disorder?

Is multiple personality "extremely rare" (*DSM-III*) or "not nearly so rare as it has commonly been thought to be" (*DSM-III-R*)? While we await definitive data, it seems reasonable to bear in mind that the two main factors which interact to produce multiple personality—child abuse and what I like to call "high dissociability" (a high ability to dissociate, which is traditionally called "high hypnotizability")—are each present in the history or cognitive style of at least 10% of the general population, meaning that the expected prevalence of multiple personality would be 1% ($10\% \times 10\%$), making it about as common as schizophrenia.

To readers who wish to find out for themselves, I suggest merely asking one additional question of the next 100 psychiatric patients that they interview (including old and new patients): Have you ever gone blank or had a memory gap, so that there were minutes or hours when you were not sure where you were and what you were doing? One must distinguish true positive answers (indicative of psychogenic, dissociative, amnesic episodes) from seizures or alcoholic blackouts, but the bigger problem will be false negative answers, which is why *DSM-III-R* omits amnesia from its diagnostic criteria for multiple personality disorder. Multiple personality patients may deny having had amnesia (for the time during which an alternate personality was in control) because they fear that "losing" periods of time means that they are hopelessly crazy or because they have "amnesia for their amnesia." Nevertheless, my own clinical experience with asking this single screening question leads me to predict that 1%–10% of the interviews will yield true positive answers and call for further evaluation.

Psychiatrists, especially those with vast clinical experience, do not believe in anything that they have not seen with their own patients. And rightly so. I used to think that articles on multiple personality disorder were interesting but had nothing to do with the real world. Finally, however, I asked some of my most puzzling and frustrating patients a different sort of question, and when their positive responses prompted me to complain that they had not told me this before, they said, "Well, doctor, you never asked."

REFERENCES

1. MacKinnon RA, Yudofsky SC: Outline of the psychiatric history and mental status examination, in *The American Psychiatric Press Textbook of Psychiatry*. Edited by Talbott JA, Hales RE, Yudofsky SC. Washington, DC, American Psychiatric Press, 1988
2. Bernstein EM, Putnam FW: Development, reliability, and validity of a dissociation scale. *J Nerv Ment Dis* 1986; 174:727-735
3. Kluft RP: The dissociative disorders, in *The American Psychiatric Press Textbook of Psychiatry*. Edited by Talbott JA, Hales

RE, Yudofsky SC. Washington, DC, American Psychiatric Press, 1988

KENNETH A. NAKDIMEN, M.D.
New York, N.Y.

Antidepressant Action of Crisis Seeking and Crisis Making

SIR: Over the years in my clinical experience, I have come to see a subgroup of patients who thrive on crises. These are people who typically "rise to the occasion" in crisis situations and do exceedingly well and also people who actively engage in creating chaos and crisis situations out of which they emerge "stronger and happier."

In the course of treating these patients who, indeed, are either crisis seekers, crisis makers, or combinations of both, it has become apparent to me that a disproportionate number of them suffer from depressive illnesses: dysthymic disorders, major depression, atypical depression, and unipolar cycling. I have begun to speculate on the potential "therapeutic efficacy" of the crises with respect to the affective disorders. Many of these people subjectively report an improvement in their symptoms both during and immediately following the crisis. One might hypothesize an influence, mediated adrenergically, possibly on endorphin metabolism that "treats" the biologically based depression. We could postulate that the response to the crisis results in a reinforcement through subjective improvement, which creates a subgroup of crisis seekers and/or crisis makers. This pattern, as maladaptive as it may appear, becomes a mechanism for inducing "self-healing." I would be interested in hearing from other colleagues who have had similar experiences. This may represent just another example of neurotic symptoms being primary and character pathology secondary.

LEWIS BRODSKY, M.D.
Tallahassee, Fla.

Alcoholics' Use of Benzodiazepines

SIR: The critical review by Domenic A. Ciraulo, M.D., and associates (1) of alcoholics' use of benzodiazepines for other than withdrawal detoxification failed to appreciate that addiction is a disease. This disease has signs, symptoms, and a chronic progressive course (2). I respect Dr. Shader and his work in psychopharmacology; however, as a psychopharmacologist who works specifically with substance-addicted patients, I feel compelled to comment on his group's article.

Using the words "putative liability" lulls the generalist into a false sense of security about alcoholic patients' use of benzodiazepines. It is an oxymoron to consider "rational therapeutic decisions" about use of an addictive substance by an alcoholic/addict. It also belies therapeutic understanding of the recovery process. Again, to state that "245 (24.5%) were using tranquilizers in a way consistent with usual practice" is an oxymoron.

Dr. Ciraulo and associates did, fortunately, profess that "alcoholics as a group may be more susceptible to benzodiazepine abuse." But I fear this is too little too late. This idea would be similar to stating that a group of methadone maintenance clients would be more likely to have illicit opiates in their urine!

What is needed at the boundary of psychopharmacology and drug abuse treatment are studies using nonaddictive

medications and receptor antagonists in prospective trials that examine relapse and recovery among recovering addicts, either medicated or medication free, but not substituting one addictive substance for another.

The concept that any physician can somehow rationally decide which alcoholic can safely use benzodiazepines is a logical impossibility to those of us actively involved in the ongoing treatment of substance addicts. To continue to persuade ourselves that this may be possible is a disservice to substance addicts as a diseased population and propagates the lack of awareness of the signs and symptoms of addiction to the general physician and general psychiatrist. Finally, it inhibits the pharmacology industry from more aggressively pursuing nonaddictive and antagonist medications. By definition, for the substance addict there can be no "better benzodiazepine."

REFERENCES

1. Ciraulo DA, Sands BF, Shader RI: Critical review of liability for benzodiazepine abuse among alcoholics. *Am J Psychiatry* 1988; 145:1501-1506
2. Kissin B: Alcohol abuse and alcohol-related illnesses, in Cecil Textbook of Medicine, 18th ed. Edited by Wyngaarden JB, Smith LH. Philadelphia, WB Saunders, 1985

WILLIAM J. ANNITTO, M.D.
Rancocas, N.J.

Dr. Ciraulo and Associates Reply

SIR: Dr. Annitto expresses the commonly held belief that alcoholics should never receive benzodiazepines. While we understand that some may have had clinical experiences which support such a conviction, we believe that neither the literature nor our clinical experience justifies such an extreme position (1). Despite serious methodological shortcomings, a substantial body of literature suggests that alcoholics are at high risk for misusing and abusing benzodiazepines, but this does not mean that all alcoholics will abuse or misuse benzodiazepines. Only after psychotherapeutic and pharmacological treatments have failed should the clinician consider treatment of the anxiety disorder with a benzodiazepine.

It is important to recognize that benzodiazepines have differing potentials for abuse. While halazepam (1) has a lower potential for abuse than diazepam in alcoholics, alprazolam may have greater risk (2). Further, benzodiazepines differ in their effects on alcohol craving and consumption and in their ability to mimic the effects of ethanol. In animal models, for example, diazepam given during withdrawal increases ethanol preference in rats, while chlordiazepoxide (3) and phenazepam (4) decrease ethanol intake.

In our experience, similar differences exist in alcoholics who receive benzodiazepines. For some, diazepam will rekindle their alcohol "high," while halazepam will not. Others have observed that chlordiazepoxide decreases craving for alcohol. To assume that all benzodiazepines have the same risk for misuse runs counter to a body of research evidence.

Dr. Annitto states that we fail to appreciate addiction as a disease. We believe that the disease concept is a pragmatic abstraction but would disagree with those who suggest that the disease concept implies one etiology or a single treatment for all alcoholics. We agree with Pattison (5), who stated, "The question of whether alcoholism is to be considered a

disease is not at debate. Rather, the issue is whether alcoholism is a unitary phenomenon or a multivariant syndrome."

We agree with Dr. Annitto that research on psychopharmacological therapy in alcoholism should continue to explore receptor antagonists and nonaddictive drugs. We remind him, however, that our paper did not support benzodiazepine maintenance therapy as a treatment for alcoholism.

Dr. Annitto somewhat glibly dismisses the possibility of a "better benzodiazepine," yet it is likely that benzodiazepines with mixed agonist/antagonist activity will have even less potential for abuse than currently available agents. Furthermore, the receptor antagonists that hold the most promise for reversing alcohol intoxication are benzodiazepines.

In conclusion, we respect Dr. Annitto's opinions, but find few data to support his position. In our program at Tufts, we see a large number of anxiety disorder patients, many of whom also have a problem with alcohol. It is undeniable that many of these patients present to us with a combined addiction to alcohol and benzodiazepines. On the other hand, there are some who find that benzodiazepines relieve their anxiety so that self-medication with ethanol is no longer necessary.

We too might use the analogy of the opioid abuser. Would Dr. Annitto withhold opioid analgesics from someone with cancer pain because that person once abused these drugs? We hope not. Is the pain of anxiety or panic any less real?

We imagine that some will continue to deny a role for medications in the treatment of alcoholics because it does not conform with their beliefs about alcoholism, but we think the matter has been inadequately studied.

REFERENCES

1. Jaffe JH, Ciraulo DA, Nies A, et al: Abuse potential of halazepam and of diazepam in patients recently treated for acute alcohol withdrawal. *Clin Pharmacol Ther* 1983; 34:623-630
2. Ciraulo DA, Barnhill JG, Greenblatt DJ, et al: Abuse liability and clinical pharmacokinetics of alprazolam in alcoholic men. *J Clin Psychiatry* 1988; 49:333-337
3. Chan AK, Leong FW, Schanley DL: Influence of chlorthalidopoxide on alcohol consumption in mice. *Pharmacol Biochem Behav* 1983; 18:797-802
4. Zakusov VV, Lyubimov I, Yavorsku AN, et al: Effect of phenazepam on ethanol intake in rats. *Bull Experimental Biology Med* 1979; 88:708-711
5. Pattison M: The selection of treatment modalities for the alcoholic patient, in *The Diagnosis and Treatment of Alcoholism*. Edited by Mendelson JH, Mello NK. New York, McGraw-Hill, 1985

DOMENIC A. CIRAULO, M.D.
BRIAN F. SANDS, M.D.
RICHARD I. SHADER, M.D.
Boston, Mass.

Interview as Part of Medical Treatment

SIR: Upon rereading my recent review of *Psychiatry and the Cinema* (1), I found that I presented unchallenged an important finding by the authors. Specifically, I echoed the authors' conclusion that "when real medical treatments (e.g., medication, ECT, lobotomy, institutionalization, hypnosis) are part of the movie, they are used in coercive, inappropriate, ineffectual, manipulative, or exploitative ways." The implication is that verbal exchange is not a *real* medical treatment. It is obvious to me that the interview is critical to and inseparable from medical care; good doctors assess cues and

verbal information given by the patient to arrive at a diagnosis and treatment plan that may or may not include tests, hospitalization, drugs, or surgery. In fact, there is considerable concern that physicians frequently neglect this phase of medical treatment. My inadvertent acceptance of this dichotomy reinforces an unfortunate impression that psychiatrists are medical doctors only when they give drugs, order tests, and do surgery.

REFERENCE

1. Ferrante J: Book review, K Gabbard, GO Gabbard: *Psychiatry and the Cinema*. *Am J Psychiatry* 1988; 145:1601-1602

JOAN FERRANTE, PH.D.
Cincinnati, Ohio

Diagnosis of Posttraumatic Stress Disorder

SIR: The current approach to the diagnosis of posttraumatic stress disorder (PTSD) is exemplified by the recent articles by Lawrence C. Kolb, M.D. (1) and Elizabeth A. Brett, Ph.D., and associates (2). Dr. Kolb explained that PTSD is a neuropsychological illness, the primary symptoms of which are due to a cortical neuronal change that subsequently leads to loss of inhibitory control of lower brainstem structures, causing symptoms of intrusion and hyperarousal. He views various avoidance behaviors and affective disturbances as being reactive to or restitutive of the primary physiological disturbance. I believe that *DSM-III-R*, in the rewriting of the criteria to include three primary categories of reexperiencing, avoidance, and hyperarousal, went too far in embracing Dr. Kolb's concept of the pathogenesis of PTSD. This concept is too narrow in light of the copious literature which supports the hypothesis that severe as well as normative trauma has a major impact on the evolution and development of human personality (3-5). More important, if we recognize that delayed PTSD is a valid entity and not just an epiphenomenon of other major psychiatric illness (depression or dementia) in a previously traumatized individual, or not just an exacerbation of a hitherto unrecognized subclinical malaise, a logical argument could be made that severe life-threatening stress has a primary effect on the personality structure of an individual. This may take the form of 1) disturbance of the sense of self, manifested by activation of primitive, unacceptable, intolerable aggression, 2) disturbance of the capacity for basic trust in the object, and 3) resulting impairment in the capacity for denial and optimism—a loss of the sense of invulnerability as well as the sense of security vis-à-vis the object world. The interpersonal experience of these individuals changes, and the ability to sustain healthy ambivalence in relationships is marred. Symptoms—if they appear, when they appear, and the form they take—would then depend on the types of defense mechanisms, of higher or lower order (6), that the ego mobilizes to cope with these primary psychological disturbances. After all, one could claim that the *DSM-III-R* symptoms of PTSD (e.g., intrusion, avoidance, and hyperarousal) which, from current estimates, appear in only about 15% of severely stressed individuals such as combat veterans are nonspecific and really no different from what might be seen in any anxiety disorder, including obsessive-compulsive disorder, phobic disorders, etc.

Thus, to head in the direction of conceptualizing PTSD primarily as a psychoneurosis is, in my opinion, a bit prema-

ture, especially as we continue to learn more about the role of childhood trauma in the genesis of adult personality disorders. Dr. Brett and associates rightly pointed out the importance of examining the relationship of PTSD to character pathology. Notwithstanding the urgency imposed by forensic and financial (e.g., compensation) concerns to come up with reductionistic criteria, there are ample clinical and research data to actually expand the diagnosis of PTSD to, perhaps, an axis II category while keeping the current axis I definition as is. A suitable model might be that of obsessive-compulsive disorder and the concomitant, although not necessarily related, obsessive-compulsive personality disorder.

REFERENCES

1. Kolb LC: A neuropsychological hypothesis explaining posttraumatic stress disorders. *Am J Psychiatry* 1987; 144:989-995
2. Brett EA, Spitzer RL, Williams JBW: *DSM-III-R* criteria for posttraumatic stress disorder. *Am J Psychiatry* 1988; 145: 1232-1236
3. Grinker RP, Spiegel JP: *Men Under Stress*. New York, McGraw-Hill, 1963
4. Brende JO: A psychodynamic view of character pathology in Vietnam combat veterans. *Bull Menninger Clin* 1983; 47:193-216
5. Erikson EH: *Identity: Youth and Crisis*. New York, WW Norton, 1968
6. Titchener JL, Ross WD: Acute or chronic stress as determinants of behavior, character, and neurosis, in *American Handbook of Psychiatry*, 2nd ed, vol. 3. Edited by Arieti S, Brody EB. New York, Basic Books, 1974

DILIP RAMCHANDANI, M.D.
Philadelphia, Pa.

Dr. Brett and Associates Reply

SIR: Dr. Ramchandani is concerned that with the creation of the hyperarousal symptom category, *DSM-III-R* "went too far in embracing Dr. Kolb's concept of the pathogenesis of PTSD." *DSM-III-R* does not endorse Dr. Kolb's view of the relationship of the reexperiencing, avoidance, and hyperarousal symptoms to each other. *DSM-III-R* merely gives a description of these three symptom clusters and asserts that they are found in PTSD. The creation of the hyperarousal category resulted from clarifying *DSM-III*'s organization of symptoms. As we pointed out in our article, inspection of the symptoms in the miscellaneous category in *DSM-III* revealed that when symptoms which actually belonged in the reexperiencing and avoidance criteria were removed, what remained were symptoms of physical arousal. The creation of the hyperarousal category makes these symptoms appear more prominent than they were in *DSM-III* but does not represent a fundamental change in their conceptualization.

Dr. Ramchandani presents an intriguing suggestion for an axis II PTSD defined by the effect on the personality of the experience of intense aggression, decreased ability to trust, and loss of the sense of invulnerability. The particular symptoms exhibited by the individual would depend on his or her ability to adapt to these primary effects of the stressor. Thus, Dr. Ramchandani is suggesting that PTSD be defined by the typical adaptive challenges a traumatic event poses to the individual, not by the resulting traits or symptoms. This is quite different from the *DSM-III-R* personality disorders, which are characterized by specific traits and behaviors. Such a PTSD would be more like the *DSM-III-R* adjustment dis-

order with its different clinical subtypes. The fact that the effect of trauma on personality can be so varied has made its conceptualization difficult. Dr. Ramchandani's suggestion is worth consideration by the *DSM-IV* committee on PTSD.

ELIZABETH A. BRETT, PH.D.
New Haven, Conn.
ROBERT L. SPITZER, M.D.
JANET B.W. WILLIAMS, D.S.W.
New York, N.Y.

DSM-III Versus DSM-III-R Criteria for Schizophrenia

SIR: Wayne S. Fenton, M.D., and associates (1) have stated that the *DSM-III-R* criteria for schizophrenia are more restrictive than the *DSM-III* criteria. We believe that their data show no difference between these two sets of criteria for schizophrenia.

These authors studied 532 patients first hospitalized at Chestnut Lodge between 1950 and 1975. Although the authors did not say, we suspect that each of the 532 patients was thought to have schizophrenia when first hospitalized. Applying *DSM-III* and then *DSM-III-R* criteria, Dr. Fenton and his colleagues found 182 and 164, respectively, of the 532 study patients to be schizophrenic. They stated that all of the 164 *DSM-III-R* patients were among the 182 in the *DSM-III* sample (i.e., 100% agreement). The authors concluded that 10% of the patients defined as schizophrenic by the *DSM-III* criteria were excluded by the *DSM-III-R* criteria.

Using the authors' data and a 2x2 contingency table to test schizophrenia versus nonschizophrenia according to *DSM-III* versus *DSM-III-R* criteria gives a chi-square, with Yates' correction, of 1.24 ($p=0.27$). Using a 2x2 contingency table to test 182 of 532 patients versus 164 of 532 patients gives a chi-square, with Yates' correction, of 0.61 ($p=0.44$). Both nonparametric analyses show no difference between the *DSM-III* and the *DSM-III-R* criteria for schizophrenia.

We suspect that the linear agreement between the *DSM-III-R* and the *DSM-III* criteria for schizophrenia is an artifact of the study design. Perhaps a more promising assessment of descriptive validity would include sensitivity, specificity, and prevalence of items (symptoms, signs, and laboratory data) according to the scales (diagnoses) in which they are placed. In analyzing these parameters, the covariation of the items with the scales would be an internal consistency (i.e., reliability) measurement (2, 3).

The authors seem to have misused the Bonferroni principle of multiple comparisons. When you make multiple comparisons using this principle, you divide 0.05 by the number of tests employed to arrive at a new significance level (4). Since they did 14 tests, they should have used a significance level of 0.0036 instead of 0.01.

Dr. Fenton and associates stated that most of their 532 patients suffered from severe and chronic schizophrenia. Since the *DSM-III* and the *DSM-III-R* criteria for schizophrenia defined, at most, 34% of the 532 patients as schizophrenic, we would like to know how they defined schizophrenia.

Some of the findings in table 1 are puzzling. Means and standard deviations for age (27.9 ± 8.0 years) were identical for the 164 patients who met the *DSM-III-R* criteria for schizophrenia and for the 18 who did not. Might this be a typographical error? Also, a mean IQ of 116 for the 18 patients failing to meet the *DSM-III-R* criteria is most unusual. We would not expect to find this mean value among a

group of college graduates. One would have to study a group of graduate students to find a mean IQ more than one standard deviation above the mean. Might this be an error in measurement?

In the editorial review of this paper in the same issue of the *Journal*, Thomas E. Gift, M.D. (5) made no comment about the statistical analysis.

REFERENCES

1. Fenton WS, McGlashan TH, Heinssen RK: A comparison of DSM-III and DSM-III-R schizophrenia. *Am J Psychiatry* 1988; 145:1446-1449
2. Baldessarini RJ, Finklestein S, Arana GW: The predictive power of diagnostic tests and the effect of prevalence of illness. *Arch Gen Psychiatry* 1983; 40:569-573
3. Widiger TA, Hurt SW, Francis A, et al: Diagnostic efficiency and DSM-III. *Arch Gen Psychiatry* 1984; 41:1005-1012
4. Godfrey K: Comparing the means of several groups. *N Engl J Med* 1985; 313:1450-1456
5. Gift TE: Changing diagnostic criteria (editorial). *Am J Psychiatry* 1988; 145:1414-1415

W.V.R. VIEWEG, M.D., F.A.C.P., F.A.C.C.
P.L. HUNDLEY, PH.D.
L.S. GODLESKI, M.D.
Charlottesville, Va.

Dr. Fenton and Associates Reply

SIR: It is possible to test the significance of the difference in the proportion of subjects diagnosed as schizophrenic by DSM-III and DSM-III-R criteria in our sample, but Dr. Vieweg and associates' chi-square formats are incorrect. They applied independent-group 2×2 chi-squares (with $N=1064$ and 1410 , respectively), but since the data are paired dichotomous ($N=532$), the correct procedure is the McNemar matched-pair chi-square (1). The value of McNemar's statistic for these matched-pair dichotomous data is $\chi^2=(18-0-1)^2/(18+0)=16.06$, $df=1$, $p<0.001$. The difference in the proportion of subjects diagnosed as schizophrenic by the two systems is statistically significant. Close reading of DSM-III and DSM-III-R reveals that the "linear agreement" between the two systems is definitional. Only the infrequent patient whose illness began after age 45 can potentially meet the criteria of the latter without also meeting the criteria of the former. There were no such patients in our sample.

Although technically correct, the application of the Bonferroni inequality by Dr. Vieweg and associates has no bearing on our findings. Whether one uses the cutoff of 0.01 or 0.0036, the conclusion is the same: DSM-III schizophrenic patients who met and failed to meet the DSM-III-R criteria are not significantly different in relation to the demographic, premorbid, or long-term outcome variables studied. Our choice of the former cutoff is the statistical equivalent of giving DSM-III-R the "benefit of the doubt" (reducing type II error), but even with this benefit, no differences were found. These data are summarized in table 1 of our paper, which contains no typographical errors. The precise mean \pm SD ages of the patients who did and did not meet the DSM-III-R criteria were 27.8720 ± 7.9640 and 27.8889 ± 8.0065 , respectively, but we would hesitate to use limited *Journal* space for routine presentation at this level of detail.

The diagnostic heterogeneity of the Chestnut Lodge follow-up study sample (Dr. Vieweg and colleagues' doubts

notwithstanding) has been described previously (2). Treated in a small, private tertiary care facility before the widespread availability of health insurance, the sample was largely homogeneous in socioeconomic status (1.5, according to the Hollingshead-Redlich scale [3]). The high IQs of our schizophrenic patients (mean=111) is consistent with their being the offspring of highly accomplished and/or affluent parents. It is interesting to note that the mean IQs for the unipolar ($N=58$) and bipolar ($N=23$) affective disorder patients in the sample were 123 and 120, respectively (4). We are often sadly reminded that high intelligence does not convey immunity to severe psychiatric disorders.

Dr. Vieweg and associates' comments raise general questions about the role of statistics in nosologic research. When application of DSM-III and DSM-III-R criteria to our sample demonstrated the latter to be narrower by 10%, we viewed this as a simple empirical result not requiring statistical elaboration. Whether the rate of schizophrenia defined by the two systems differs in a clinically (as opposed to statistically) significant way will, of course, depend on the size and nature of the sample studied and the utility of the diagnosis. A follow-up study of autistic children as adults, or calculation of the national financial impact of schizophrenia, for example, would be affected substantially; evaluation of emergency room admissions over a month's time, less so. Statistical tests can help inform common sense in research, but cannot be used as a substitute for it.

REFERENCES

1. Fleiss JL: Statistical Methods for Rates and Proportions, 2nd ed. New York, John Wiley & Sons, 1981, pp 112-119
2. McGlashan TH: The Chestnut Lodge follow-up study, I: follow-up methodology and study sample. *Arch Gen Psychiatry* 1984; 41:573-585
3. Hollingshead AB, Redlich FC: Social Class and Mental Illness: A Community Survey. New York, John Wiley & Sons, 1958
4. McGlashan TH: The Chestnut Lodge follow-up study, II: long-term outcome of schizophrenia and the affective disorders. *Arch Gen Psychiatry* 1984; 41:586-601

WAYNE S. FENTON, M.D.
THOMAS H. MCGLASHAN, M.D.
ROBERT K. HEINSEN, PH.D.
Rockville, Md.

Minimal Cultural Experiences in Psychiatric Training

SIR: I would like to commend Joel Yager, M.D., and associates (1) for attempting to delineate minimal clinical experiences for psychiatric residents. Institution of such standards would surely help us to develop well-rounded, competent psychiatrists.

However, I would like to suggest that one category be added to their list in some kind of way. Although one socio-demographic variable (i.e., age) was included, it is curious that another broad sociodemographic variable (i.e., culture) was ignored. Over the past 15 years, despite training requirements and recommendations that have repeatedly called for appropriate education in cultural psychiatry, in practice, psychiatric residency programs have fallen far short of this goal (2, 3). If the cultural variable is ignored in any proposed national standards for psychiatric training, this educational deficit is likely to remain, along with the ensuing compromised care of many cultural groups in the United States.

How might the cultural component be added to any na-

tional standards? In contrast to exposure to patients of different ages, it may not be so easy to designate a certain number of exposures to patients from different cultural groups. One simple reason is that some programs may not have patients from a variety of cultural backgrounds because of local population variations. So while it may be ideal to designate that each resident have two long-term psychotherapy patients from each of our major ethnic groups—black, Hispanic, Asian, and white—that possibility may not be omnipresent. Instead, the cultural requirements may need to be more general and be derived from the generic principles of education in cultural psychiatry (2, 3). If culture is thereby viewed broadly, to include racial, ethnic, religious, sexual, social class, and possibly even age factors, it may be easier to specify cultural clinical experiences. For example, each resident might be required to have two long-term psychotherapy patients from cultural backgrounds very different from that of the resident. Psychotherapy is emphasized because of the influence of this more intense interpersonal experience on one's values, countertransference, and stereotypes. Related requirements might be made for evaluation and other treatment modalities.

REFERENCES

1. Yager J, Borus JF, Robinowitz CB, et al: Developing minimal national standards for clinical experience in psychiatric training. *Am J Psychiatry* 1988; 145:1409–1413
2. Moffic HS, Kendrick EA, Lomax JW, et al: Education in cultural psychiatry in the United States. *Transcultural Psychiatr Research Rev* 1987; 24:167–187
3. Moffic HS, Kendrick EA, Reid K, et al: Cultural psychiatry education during psychiatric residency. *J Psychiatr Education* 1988; 12:90–101

H. STEVEN MOFFIC, M.D.
Houston, Tex.

Dr. Yager and Associates Reply

SIR: We are delighted that Dr. Moffic reminded us to add cultural issues to the process of developing national standards for minimal clinical experiences. We have all been concerned that cultural diversity and transcultural clinical experiences be part of every resident's training activities. As Dr. Moffic points out, even though the nature of this experience will vary from program to program according to local conditions, the necessity of ensuring that all trainees have some supervised clinical experience with patients from other cultures and backgrounds should be an explicit part of any standard set of national expectations for training.

JOEL YAGER, M.D.
Los Angeles, Calif.
JONATHAN BORUS, M.D.
Boston, Mass.
CAROLYN B. ROBINOWITZ, M.D.
Washington, D.C.
JAMES H. SHORE, M.D.
Denver, Colo.

Trends in the Treatment of Depression

SIR: The recent article by Darrel A. Regier, M.D., M.P.H., and colleagues (1) provided an informative overview of the

National Institute of Mental Health (NIMH) Depression Awareness, Recognition, and Treatment Program. The rationale for this educational program rests to a considerable degree on the Epidemiologic Catchment Area Program finding that large numbers of depressed persons go untreated (2). Although untreated depression is an issue of major clinical and public concern, data from the National Ambulatory Medical Care Survey suggest that the outpatient care of depressed patients has significantly increased in recent years.

The National Ambulatory Medical Care Survey is a national survey of physician activity conducted by the National Center for Health Statistics. Because the survey is confined to office-based physicians, it does not measure the care provided by nonpsychiatrist mental health professionals or physicians working outside office-based settings. Periodic modifications in the diagnostic system also limit analysis of longitudinal trends. With these caveats in mind, the National Ambulatory Medical Care Survey found that the number of visits to psychiatrists for depression increased 77% between 1975 and 1985 (3). Whereas there were 3.0 million visits to psychiatrists for depression in 1975 (19.6% of all visits to psychiatrists), the number grew to 5.3 million by 1985 (29.4% of all visits to psychiatrists). The number of visits to internists for depression more than doubled during this time period (377,723 in 1975; 822,157 in 1985) (unpublished data from the survey). Although the outpatient treatment of depressed patients by general and family practitioners declined slightly between 1975 and 1985, it substantially increased as a percentage of total general and family practice visits (unpublished data from the survey).

The source of the recent growth in outpatient treatment of depressed patients remains unclear. Perhaps this growth reflects an expanding public awareness of depressive symptoms. The public may be becoming more knowledgeable about depression and accepting of its treatment by health professionals. Increased professional interest may also be leading to greater recognition and therefore treatment. This may be particularly true in the general medical sector, where depression and other mental disorders commonly present as physical rather than psychological symptoms (4). If such changes are occurring, the NIMH Depression Awareness, Recognition, and Treatment Program will discover pre-existing momentum as it drives to increase the quality and availability of care provided to persons with depressive disorders.

REFERENCES

1. Regier DA, Hirschfeld RMA, Goodwin FK, et al: The NIMH Depression Awareness, Recognition, and Treatment Program: structure, aims, and scientific basis. *Am J Psychiatry* 1988; 145: 1351–1357
2. Shapiro S, Skinner EA, Kessler LG, et al: Utilization of health and mental health services: three Epidemiologic Catchment Area sites. *Arch Gen Psychiatry* 1984; 41:971–978
3. Gardocki GJ: Office Visits to Psychiatrists: United States, 1985: Vital and Health Statistics, series 13, number 94. Washington, DC, National Center for Health Statistics, 1988
4. Schurman RA, Kramer PD, Mitchell JB: The hidden mental health network: treatment of mental illness by nonpsychiatrist physicians. *Arch Gen Psychiatry* 1985; 42:89–94

MARK OLFSON, M.D.
New Brunswick, N.J.

Dr. Regier and Associates Reply

SIR: We hope that Dr. Olfson's optimism about improved treatment of depression is warranted, but we doubt that the data he quotes from the National Ambulatory Medical Care Survey prove that point.

First, he quotes the percentage of psychiatric visits made by patients with a principal diagnosis of depressive disorder as increasing from 19.6% in the 1975 survey to 29.4% in the 1985 survey. Those two surveys used different classification systems—*ICDA-8* and *ICD-9-CM*, respectively. An intermediate survey in 1980–1981, which also used *ICD-9-CM*, had already found the increase from 1975, with 26.8% of psychiatric visits made by patients with a principal diagnosis of depressive disorder. These findings from the 1980–1981 survey are presented in the publication Dr. Olfson referenced, but he did not mention them. As indicated in that publication's discussion of the three surveys, the findings suggest that the availability of new categories such as major depressive disorder in *ICD-9-CM* may be responsible for the reported increase in depressive diagnoses in 1980–1981 and 1985, as well as for the corresponding decrease in coding other categories such as neurotic disorders. In this context, it should be remembered that very large surveys like the National Ambulatory Medical Care Survey are not able to perform independent assessments of the patients to verify the diagnoses reported by participating clinicians.

Second, Dr. Olfson's effort to infer information about treatment from survey data on diagnosis is not one we recommend. The NIMH Collaborative Study on the Psychobiology of Depression has shown that patients with serious cases of depression are often not properly treated even when diagnosed (1). Underrecognition or misdiagnosis of affective disorders has been found in at least some specialty settings

(2), in addition to the primary care facilities we reported in our original paper.

Third, prior analyses of the 1980–1981 and 1985 survey data have demonstrated that a diagnosis of mental disorder is not strongly associated with the treatment provided. Analysis of the 1980–1981 data found that in primary care, the majority of psychotropic drugs were prescribed without an associated diagnosis of mental disorder (3). These findings were confirmed by the 1985 survey data (unpublished 1988 paper by D.B. Kamerow and A.A. Hohmann).

For these reasons, we hesitate to accept Dr. Olfson's view that patients with depression have been presenting more commonly for outpatient care, and we do not have any credible evidence of a trend toward improved treatment. Obtaining these data for evaluating the effectiveness of the Depression Awareness, Recognition, and Treatment Program is important, but we do not underestimate the difficulty of that task.

REFERENCES

1. Keller MB, Klerman GL, Lavori PW, et al: Treatment received by depressed patients. *JAMA* 1982; 248:1848–1855
2. Lipton AA, Simon FS: Psychiatric diagnosis in a state hospital: Manhattan State revisited. *Hosp Community Psychiatry* 1985; 36:368–373
3. Jencks SF: Recognition of mental distress and diagnosis of mental disorder in primary care. *JAMA* 1985; 253:1903–1907

DARREL A. REGIER, M.D., M.P.H.
ROBERT M.A. HIRSCHFELD, M.D.
FREDERICK K. GOODWIN, M.D.
JACK D. BURKE, JR., M.D., M.P.H.
JOYCE B. LAZAR, M.A.
LEWIS L. JUDD, M.D.
Rockville, Md.

Reprints of letters to the Editor are not available.

Correction

The names listed below were inadvertently omitted from the Editor's "New Year's Greetings" (January 1989 issue, pp. 2-7), which is partially reprinted here:

New Year's Greetings

"If men could learn from history," remarked Samuel Taylor Coleridge, "what lessons it might teach us! But passion and party blind our eyes, and the light which experience gives is a lantern on the stern, which shines only on the waves behind us!" True enough, but in his moment of transient cynicism Coleridge overlooks the pleasures of reflective reminiscence—a pleasure in which the Editor annually indulges as the year comes to an end and another volume of the *Journal* is completed. Shuddering momentarily at the recollection of the myriads of manuscripts that have crossed his desk in seemingly endless procession, he soon remembers the hundreds of colleagues who, in selfless anonymity, have helped him in their capacity as reviewers; and his spirits rise in the realization that the time has at last come to express his deep gratitude for their invaluable contributions to their profession and their *Journal* during the period from November 1, 1987, to October 31, 1988.

Robert L. Arnstein, M.D.

Jonathan E. Kolb, M.D.

Roslyn Seligman, M.D.

Frederick K. Goodwin, M.D.

Bennett L. Leventhal, M.D.

Monica N. Starkman, M.D.

Paul N. Graffagnino, M.D.

Allan F. Mirsky, Ph.D.

Peter E. Stokes, M.D.

Daniel R. Hanson, Ph.D., M.D.

Arthur J. Prange, M.D.

Fridolin Sulser, M.D.

Leston L. Havens, M.D.

Eric M. Reiman, M.D.

Ilza Veith, Ph.D., M.D.

Michael Irwin, M.D.

Maj-Britt Rosenbaum, M.D.

Andrew S. Watson, M.D.

Michael Jellinek, M.D.

J.C.N.

Employee Assistance Programs and the Role of the Psychiatrist: Report of the Committee on Occupational Psychiatry

This report was prepared by the Committee on Occupational Psychiatry¹ of the Council on National Affairs. It was approved by the Board of Trustees in December 1988.

The 1984 "Report of the Task Force on Psychiatry and Industry" (1) urged psychiatrists to both examine their role and become involved in occupational settings. That report, which drew on the experience of the task force members and on the literature, attempted to acquaint APA members with potential roles for psychiatrists in occupational settings and to identify some of the special considerations associated with moving psychiatry back into the workplace. The task force promised this second report, a report devoted exclusively to employee assistance programs (EAPs) and the role of the psychiatrist in this new model for the delivery of mental health services in occupational settings.

The influence of EAPs, an increasingly popular way for employers to assist troubled employees, has expanded considerably (2-10). Both the number of programs sponsored by employers and the range of services included in these programs have grown rapidly. EAPs now influence the types and quality of mental health services available to a significant segment of the nation's work force, as well as how employees and their families gain access to these services. However, few psychiatrists are currently involved in this rapidly growing and significant form of mental health service delivery, either in a part-time or full-time capacity (11).

In its effort to determine the optimal role of the psychiatrist in EAPs and to promote the involvement of psychiatrists, in this report the Committee on Occupational Psychiatry first presents some background information, focusing on the history and development of EAPs and on the need for EAPs and their potential cost savings to employers. The report moves on to the structure and function of EAPs and to the role of psychiatrists and some problems psychiatrists may encounter in their work in EAPs. In concluding, the committee identifies some APA activities intended to increase the participation of psychiatrists in EAPs.

BACKGROUND

EAP History and Development

Today's EAPs grew out of the employee counseling movement that began at the turn of the century. The programs were initiated at

a few companies in the 1920s but gained little ground in the subsequent two decades. Training in occupational mental health expanded somewhat during the 1950s, but it was not until the 1960s and 1970s that American business began once again to devote more attention to troubled employees (11).

Employees experiencing problems with alcohol were the initial focus of the new EAPs. In 1970 the comprehensive federal Alcohol Abuse and Alcoholism Treatment and Rehabilitation Act required federal agencies and military commands to institute alcoholism programs. The occupational programs branch of the National Institute on Alcohol Abuse and Alcoholism provided guidance and support to organizations willing to establish counseling programs for employees experiencing problems with alcohol. Over time EAPs were extended to include troubled employees whose work performance was affected adversely by a variety of personal problems, some of which were symptomatic of covert psychiatric illness (11).

Approximately 2,000 EAPs were established in businesses in the United States between 1972 and 1982. By 1984 the total number had increased to 8,000 (12). More than half of the largest companies in the United States now operate EAPs, providing alcoholism services alone or in combination with clinical counseling and a variety of other services for troubled employees (8).

The December 1987 issue of *Eco-Facts*, the newsletter published by APA's Office of Economic Affairs, contained the findings of a survey of 293 companies of various sizes and industry types conducted by Hewitt Associates to elicit prevailing patterns of mental health benefits and company-sponsored EAPs (13). As of June 1986, nearly half of the companies had EAPs, and over one-third had been implemented since the beginning of 1984. The average usage rate was 6% for first-year EAPs and 7% in succeeding years. Asked to indicate their most important reason for providing mental health coverage, 37% of the companies cited "moral obligation," 35% cited "competitive practice," and 15% indicated "cost management for over-all medical plan." Also identified were "employee demand" (6%), "part of medical plan" (4%), and "employee productivity" (1%).

Nearly all (99%) of the EAPs in the companies surveyed by Hewitt covered substance abuse. The percentages for other conditions were as follows: mental and nervous disorders, 92%; marital and family discord, 91%; stress, 83%; financial problems, 81%; legal problems, 72%; job performance, 69%; eating disorders, 63%; termination, 33%; and retirement, 28%. Psychiatrists were the practitioners most frequently eligible for reimbursement; 98% of the 288 reporting plans reimbursed psychiatrists (13).

The Need for EAPs and Their Potential Cost Savings

A troubled employee can be defined as an individual whose work performance is impaired by personal problems, including conflicts with supervisors, peers, or subordinates; absenteeism; substance abuse; family or marital discord; and financial or legal problems. In a significant number of instances, these personal problems are symptomatic of an undiagnosed psychiatric disorder (11).

The few studies reported in the literature, some of which suffer

¹The committee included Duane Q. Hagen, M.D. (chairperson), Barrie S. Greiff, M.D., Alan A. McLean, M.D., Peter Boxer, M.D. (corresponding member), Daniel Amen, M.D. (corresponding member), Jeffrey Speller, M.D. (corresponding member), Peter L. Brill, M.D. (consultant), Leonard M. Moss, M.D. (consultant), and Lester I. Debbold, M.D. (APA/Burroughs Wellcome Fellow).

from poor experimental design, improper sampling techniques, and inappropriate statistical analysis, indicate that 10% to 25% of the actual work force suffer from personal problems, overt or covert psychiatric illness, or both (11). Follmann (14) cited several specific findings: 1) a large insurance company which underwrites employee disability insurance reported that 5.7% of all long-term disability claims were submitted by employees suffering from mental disorders, 2) the National Center for Health Statistics reported that a significant percentage of the working population exhibit psychological symptoms, and 3) in a study conducted at Cornell University, the potential for emotional instability among industrial workers was estimated to be between 20% and 25%.

Carr and Hellan (15) found that 10% to 12% of the work force in the United States experience serious personal problems and that a significant number of these workers suffer from alcoholism or other chemical dependence. Kuzmits and Hammons (16) estimated that 10 million workers suffer from the effects of alcohol abuse or dependency. In addition, they cited a 1971 survey by the National Industrial Conference Board of New York, which found that 53% of 222 employers reported drug use among their employees.

It is difficult to gather reliable empirical data on the overall economic cost of troubled employees to their employers. The results of cost-effectiveness studies of EAPs are inconclusive, yet a variety of studies have demonstrated net cost savings. The authors of one study (17) reported a 52% improvement in attendance among troubled employees of Kennecott Copper Corporation who had sought help for their personal problems from the company's EAP counselor. Work compensation and health care costs for the employees decreased by 74.6% and 55.4%, respectively.

Cost savings also have been demonstrated in controlled studies of utilization of medical benefits by employees with access to EAPs (18). The Gates Rubber Company saved approximately \$56,000 one year when medical visits to the company clinic fell 43% (19). Other companies have reported a 46% decrease in sickness disability payments, a 39% decrease in disability payments, and a 52% reduction in grievances and disciplinary actions for employees in their respective EAPs (20). These data are consistent with studies that show a decreased use of medical services after mental health interventions. Jones and Vischi (18), in their comprehensive review of 22 studies, some in occupational settings, reported a general decline in the use of general medical services after mental health intervention. The decline ranged from 5% to 85%.

Walsh (21), in a discussion of the employer's responsibility to sponsor counseling for troubled employees, asked if employers are responding to a bandwagon effect with regard to initiating EAPs. Leonard Moss, M.D., presenting the view of APA's Task Force on Psychiatry and Industry at the workshop "Role of Psychiatrists in EAPs" (140th APA annual meeting, 1987), emphasized that well-conceived, effective mental health services for troubled employees benefit both employer and employee. He added that coping with personal and family problems endemic to the human condition may be the individual's responsibility but that when work-related stress plays a role in the genesis or exacerbation of such problems, management needs to be aware of it and provide assistance.

STRUCTURE AND FUNCTION OF EAPs

Employee assistance, or employer-sponsored counseling for troubled employees, has become accepted management practice in most of the nation's largest work organizations. Employers provide some form of confidential counseling to employees for personal problems that might influence their ability to work effectively. To manage employees with deteriorating work performance, confidential counseling on personal issues and personnel policies are integrated. Frequently, employee assistance personnel make decisions regarding medical disability, the adequacy of outside treatment, and employee readiness to return to work. Management at times relies on the employee assistance function to help manage the human aspect of organizational change.

Structure

An EAP is either internal or external to its sponsoring organization (22). An internal EAP is part of the personnel or medical department of the work organization. Generally, full-time in-house professionals staff an internal EAP. According to a survey by Lewis of 68 Chicago businesses with EAPs, 78% had internal programs (23).

An external EAP, a free-standing organization, provides services to a sponsoring organization on a contractual basis. Responding to the increasing demand for employee counseling, several kinds of organizations have begun to offer EAPs to industry. These include, among others, consulting firms, physician groups, hospitals, community mental health centers, and family service agencies. It is estimated that more than 100 consulting firms offer EAP services (24). Smaller employers often join a consortium of other companies to contract as a group with a single EAP to provide counseling services for their employees.

Vendors also offer management program development and implementation services in addition to services designed to help the employee. These include consultation on developing company policies and procedures, shaping a program to fit organizational needs, and training supervisors in the use of the program.

Programs to provide employee assistance vary considerably in the types of problems addressed, the formality of policies and procedures, the locus of the program in the medical or personnel department or in an outside contractor group, program staff, and the use of outside treatment resources. Nonetheless, a basic EAP model emerges. Of major importance is that many of these programs are now serving a gatekeeper function, providing case management and directing services on a preferred provider basis, often excluding psychiatrists. When psychiatrists are excluded from these programs, there is a significant risk of inadequate assessment, inaccurate diagnosis, and unnecessary or harmful treatment.

Function

Troubled employees come to the attention of EAP professional staff through either self-referral or referral by management on the basis of impaired work performance. A "coordinator" is available to employees to define the nature of an employee's problems and to recommend to the employee appropriate resources for assistance. Coordinators may perform a triage function only, evaluate the presenting problem, or even provide short-term counseling and then refer the employee for further assistance, if necessary. The coordinator also serves as a liaison between employee and community resources and between employees and management. The role of the coordinator is critical to the outcome of the employee assistance process. The initial assessment of the employee's problem may be performed by in-house staff, a vendor group, or a professional in the community; regardless, the background and professional training of the coordinator influences the perception and evaluation of the employee's problems and the referral for further assistance.

Acknowledging employees' fears that their personal problems may become known to others in the organization, most EAPs consider confidentiality as necessary for program success and maintain separate records on their clients. To handle specific problems that call for coordination with supervisors or others in the organization, the employee signs a release-of-information statement (11). Of the 68 Chicago companies surveyed by Lewis (23), 70% indicated that they received reports on an employee's cooperation and overall progress only after the employee had signed such a statement.

Most EAPs provide one of four categories of services: alcohol and substance abuse, information and referral, executive and employee counseling, and comprehensive. The services offered by the EAPs in the 293 companies surveyed by Hewitt (13) were as follows: off-site counseling through a private provider (64%), short-term outpatient counseling (53%), employee assessment and referral only (43%), on-site counseling (employer-based) (34%), inpatient hospitalization (26%), and long-term outpatient counseling (18%).

As indicated, alcohol and substance abuse programs have the longest history. Even today, a significant percentage of the troubled employees who consult EAPs present alcohol or other substance

abuse as their problem (22, 25). Frequently, persons recovering from alcoholism who have strong ties to Alcoholics Anonymous operate alcohol and substance abuse EAPs (21, 26).

Information and referral services may take a broader approach to employee assistance and may refer clients to a wide variety of resources covering legal, financial, housing, family, marital, alcoholic, and psychiatric problems. Some EAPs refer employees only for psychological needs. Often, more than half of the employee requests to information and referral programs are handled over the telephone (11).

Executive and employee counseling programs contract with organizations to provide a fixed, maximum number of counseling sessions per employee. Employees in need of more extensive counseling or psychotherapy are referred to outside professionals. Executive and employee counseling programs deal with all forms of emotional and personal problems appropriate to the counseling mode. They provide short-term psychotherapy and offer help for specific and readily responsive problems. Employees with alcohol and substance abuse problems are referred to residential or outpatient treatment agencies (11).

The comprehensive EAPs focus on prevention as well as a full range of employee problems and, consequently, employ a multidisciplinary professional staff geared toward viewing an individual from various perspectives. Comprehensive EAPs usually offer prevention programs on stress management, wellness, and nutrition in addition to the more traditional assessment and treatment services (11).

The present atmosphere of organizational transition and the escalating costs of mental health care are motivating employers to reassess both the cost-effectiveness of EAPs and their function within the organizational development plan. A "proactive" approach to the redesign of EAPs is emerging. Employers look to the employee assistance function to help realize specific organizational goals: 1) providing humane management of job insecurity and job loss associated with work force reduction and organizational restructuring, 2) buffering the extraordinary pressures of major organizational change and maintaining the stability of the surviving organization after change has occurred, 3) achieving cost benefits from prevention and early intervention in development of work/stress-related physical and emotional disorders, and 4) controlling mental health care costs by redesigning the benefits and services available both in-house and in the community.

THE PSYCHIATRIST'S ROLE

In its 1984 report, the Task Force on Psychiatry and Industry considered the question of the optimal role of the psychiatrist in EAPs. Recognizing that no two programs or settings are identical, the task force concluded that there is no single role for the psychiatrist and identified important facts about EAPs which must be considered: 1) the model program identifies individuals with a broad mixture of problems, some of which are serious or even life-threatening, 2) the task of confronting an individual with serious questions about job performance or job security needs to be approached with great sensitivity to both the individual and the situation, and 3) decisions about the referral of clients to appropriate resources must be considered carefully.

The task force acknowledged the role other disciplines play in EAPs and encouraged psychiatrists to become familiar with the skills and capabilities of these other mental health professionals. The task force also noted, "Sometimes well-meaning individuals who are not medically qualified and who are working with EAPs make major medical and treatment decisions for which they lack adequate background—with possibly serious consequences." The New York State Council on Alcohol Problems issued a position paper on EAPs, in which it also expressed concern about the qualifications of all EAP professionals to provide treatment, noting that credentialing in the EAP environment is not as stringent as in the treatment community.

Brill et al. (11) noted that most EAP staff have earned either a bachelor's or a master's degree in a mental health discipline, such as counseling psychology, clinical social work, or nursing. Lewis's Chicago-based study (23) found that 30% of EAPs are managed by

individuals with bachelor's degrees and 65% by persons with master's degrees. Psychiatrists were responsible for less than 1% of all employees covered. There is reason to be concerned that without the medical training and expertise of psychiatrists, EAPs risk missing significant medical and psychiatric illnesses. In Koranyi's study of more than 2,000 psychiatric clinic patients (27), he found that 43% of the patients had major medical illness, and 10% had medical illnesses that accounted totally for their "psychiatric" symptoms. Koranyi also reported that psychologists and social workers missed these illnesses 50% more often than did psychiatrists.

On this basis, the Task Force on Psychiatry and Industry considered psychiatrists to have a crucial role in determining how to make EAPs as effective and as sound as possible. They stated that it is appropriate and advisable for psychiatrists to be involved in planning the EAP to assure the necessary backup and that the confidentiality policies pertaining to program users should be clear and explicit.

Minimally, every program requires a psychiatric consultant whose supervisory involvement is sufficient to assure that client needs are served optimally (1).

Additionally, psychiatrists can serve a useful role in the selection and orientation of the program coordinator, can be available on an ongoing basis to assist the coordinator in the assessment of difficult cases, and can ensure that clients are referred to resources which will provide optimal help or treatment for their problems. The task force stated that psychiatrists can and should go further by developing educational materials for the training, skills development, and support of occupational health professionals (1).

Brill et al. (11) reported that the literature contains little information on the role of the psychiatrist as a specific and integral part of an EAP. They included and discussed case illustrations from their experiences in establishing and operating a comprehensive external EAP, conducting research on mental illness in the workplace, consulting to industry and government EAPs, and providing clinic services to employees who are emotionally disturbed. On the basis of their collective experience, they identified a variety of roles the psychiatrist can assume in an EAP, a few of which the Task Force on Psychiatry and Industry specified in its 1984 report.

The Psychiatrist as Clinician

In the role of full- or part-time clinician, the psychiatrist performs evaluations, provides short-term psychotherapy, and refers clients to outside agencies for more intensive treatment. The psychiatrist works in this role to ensure that the troubled employee obtains competent triage, disposition, and treatment where indicated. It is particularly important that the psychiatrist-clinician determines whether a psychopathology underlies the more common legal, financial, or marital complaints a troubled employee presents.

As a physician, the psychiatrist is the only member of the team who is fully trained and qualified to distinguish medical from psychiatric illness and also is most qualified in the complex task of diagnosing psychiatric problems that may be determining factors in dysfunctional behaviors in the workplace. Along with these unique skills, the psychiatrist understands the underlying individual, family, and group dynamics that are important determinants in formulating an effective treatment plan in any given case.

Other duties of the psychiatrist in the role of clinician include conducting psychiatric examinations to determine fitness for duty or specific assignments, eligibility to receive medical disability payments for psychiatric reasons, and need for psychotropic medications. To avoid the appearance of a conflict of interest, troubled employees who require further counseling usually are not referred to the psychiatrist's own outpatient practice.

The Psychiatrist as Supervisor and Educator

In the role of clinical supervisor, the psychiatrist oversees the clinical work of nonphysician mental health professionals and clinical counselors. Frequently, the psychiatrist meets with other EAP staff to review cases presenting difficulties and to provide guidance, advice, and support to those managing such cases. Whenever necessary, the psychiatrist meets with an employee to obtain firsthand knowledge

of a case, but the final disposition usually is left to the EAP counselor. Psychiatrists understand the medicolegal obligations of case supervision and can help design the case management process to optimize assessment and staffing functions so that troubled employees get the best care and members of the staff get proper supervision and opportunities for education.

In the role of educator, the psychiatrist conducts in-service seminars and case conferences for the EAP and staff. These seminars and conferences focus on increasing the staff's sophistication in recognizing the signs and symptoms of mental illness and their knowledge of its course and treatment. Another purpose of the seminars is to teach managers and supervisors to judge how and when to refer employees to an EAP. Seminars also may address more general topics, such as stress management, marital disharmony, adolescent drug abuse, personal financial management, career development, alcoholism, and primary prevention and mental health promotion in the workplace.

The Psychiatrist as Administrator

As administrator, the psychiatrist works to maintain the quality of services provided to troubled employees. This involves grappling with the management concerns of budgeting, payroll, accounting, finances, long-range planning, marketing, clinical program development, and personnel. For example, Dr. Peter Brill, Director of the Center for Study of Adult Development, a comprehensive external EAP, is responsible for structuring client evaluations, referring and tracking clients, training employees and supervisors, and generating program material. He also supervises the work of other EAP staff, including the psychiatrist responsible for the day-to-day clinical supervision of the program's counselors and administrative and management staff. As director, Brill also oversees the administrative tasks of payroll and general accounting, budgeting and forecasting, financial and strategic planning, recruiting, and hiring.

The Psychiatrist as Organizational Consultant

The psychiatrist, by virtue of his or her expertise in intrapsychic, interpersonal, and systems issues, is in an excellent position to consult with middle and senior management about their interpersonal and organizational problems. One example of how the psychiatrist might function in this role is the psychiatrist who helps an organization adjust to the loss of a respected senior executive by fostering an appropriate mourning process and thereby facilitating a smoother transition between administrators. Other functions of the psychiatrist at work in this role include helping senior management staff to better understand their own limitations and the ways in which they can avoid introducing their own intrapsychic conflicts into the workplace and helping middle and senior managers in industry to examine their organizational culture and work practices with the goal of improving employee productivity and job satisfaction. The latter, in turn, benefits the mental and physical health of employees.

PROBLEMS PSYCHIATRISTS ENCOUNTER IN EAPS

One of the problems a psychiatrist encounters in an EAP concerns confidentiality. The psychiatrist is employed to protect the interests of both the patient/client and the organization. This requires the psychiatrist to balance constantly the patient/client's need for confidentiality against the organization's need for information that will assist it in the proper management of employees.

Remuneration emerges as another problem area. The psychiatrist who works as an EAP clinical consultant frequently is reimbursed at an hourly rate far below that usually provided for individual psychotherapy conducted in private practice. Even a psychiatrist who is an organizational consultant is rarely reimbursed at a rate commensurate with that provided to private practitioners of individual psychotherapy.

A third problem area relates to conflicting goals within the organization. The psychiatrist consultant is called on to manage conflicts between the medical department, which is concerned about the pa-

tient's clinical status and needs, and the personnel department, which is concerned about treatment costs and staffing needs of the organization.

The psychiatrist's own need for some education in the role of a psychiatric consultant may emerge as a potential problem. A review of the literature on crisis management and short-term therapy is a helpful start for most beginning consultants.

Finally, the psychiatrist who participates in an EAP must be prepared to experience the inevitable frustration of dealing with organizational procedures and policies that may hinder the recovery of troubled employees or exacerbate their conditions (11).

SUMMARY AND RECOMMENDATIONS

There is no single, optimal role for the psychiatrist in EAPs. The roles of clinician, supervisor/educator, administrator, and organizational consultant all are avenues of involvement open to the psychiatrist. And, as Brill et al. (11) remind us, "Appropriate involvement in an employee assistance program will enable psychiatrists to contribute significantly to the task of providing high-quality care to troubled employees so that they can once again become productive and satisfied in the workplace."

Further, increased involvement on the part of psychiatrists in EAPs will emphasize the growing influence of this significant new model for the delivery of mental health services. The work setting of the 1980s and 1990s provides opportunities for creative approaches to occupational mental health issues and opens the door for the psychiatrist to work collaboratively with individuals representing management, human resources, and other mental health disciplines and to apply psychiatric skills in shaping the generation of EAPs. Although there is no single optimal role for psychiatrists in EAPs, their involvement is essential if this expanding mental health care delivery model hopes to adequately serve the needs of the troubled employee.

There is an optimal role in EAPs for APA, its Committee on Occupational Psychiatry, and its district branches. That role is to increase the participation of psychiatrists in EAPs and to further facilitate their involvement. Following are some of the efforts toward this end that have been made within APA.

Activities

An issue workshop, "Role of Psychiatrists in EAPs," was held at the 1987 APA annual meeting. The workshop's educational objectives were to identify at least four roles of psychiatry within EAPs, to respond to divergent viewpoints on hiring psychiatrists in EAPs, to recognize issues considered to be conflicts of interest related to treatment, and to identify which role within EAPs, if any, meets individual career objectives. A related workshop, "Psychiatry at Work," was held at the 1988 APA annual meeting. The APA Committee on Occupational Psychiatry is planning additional workshops for future meetings and is working on a long-range plan to increase the number of psychiatrists with occupational orientations and to increase opportunities for psychiatrists already working in this field to meet and exchange ideas.

The Committee on Financing and Marketing has set 1989 as its target date for the publication of "Developing Employee Assistance Program Relationships," its step-by-step guidelines for district branches. The overall objective is to develop a strong, positive, and productive relationship between a district branch and an EAP or employer—to make local businesses aware of the psychiatric resources in the community and to encourage referrals to these resources, as appropriate, on the part of EAPs and other corporate sources. The creation of a strong and positive relationship between a district branch and an EAP or employer is viewed as a long-term investment, which can help ensure psychiatric input into referrals and decisions about benefits for the purpose of maintaining the availability over time of high-quality, affordable psychiatric services.

REFERENCES

1. American Psychiatric Association Task Force on Psychiatry and Industry: Report of the Task Force on Psychiatry and Industry. *Am J Psychiatry* 1984; 141:1139-1144
2. Hollman RW: Managing troubled employees: meeting the challenge. *J Contemporary Business* 1980; 4:43-57
3. Muldoon JA, Berdie M: *Effective Employee Assistance*. Minneapolis, Multi-Resource Centers, 1978
4. Smejda H: How one hospital sells its expertise to industry. *Hospital Financial Management* 1977; 31:8-12
5. Schneider P: There is a better way to help troubled employees. *The Office* 1979; 89:46-50
6. Featherston JH, Bednarek RJ: A positive demonstration of concern for employees. *Personnel Administrator* 1981; 26:43-47
7. Wagner WG: Assisting employees with personnel problems. *Personnel Administrator* 1982; 27:59-63
8. Dickman F, Emener WG: Employee assistance programs: basic concepts, attributes, and an evaluation. *Personnel Administrator* 1982; 27:55-58
9. Emener WG, Dickman F: Corporate caring. *Management World* 1983; 12:36-38
10. Hellan RT: Employee assistance programs. *Management World* 1980; 9:18-20
11. Brill P, Herzberg J, Speller JL: Employee assistance programs: an overview and suggested roles for psychiatrists. *Hosp Community Psychiatry* 1985; 36:727-731
12. Roman PM: Pitfalls of "program" concepts in the development and maintenance of employee assistance programs. *Urban and Social Change Rev* 1983; 16:9-12
13. Hewitt study details mental benefits. *Eco-Facts*, Dec 1987, pp 1, 9
14. Follmann JF Jr: *Helping the Troubled Employee*. New York, AMACOM, 1978
15. Carr JL, Hellan RT: Improving corporate performance through employee assistance programs. *Business Horizons* 1980; 23:57-60
16. Kuzmits FE, Hammons HE II: A healthy, effective work force is still management's most valuable resource. *Personnel J* 1979; 58:239-250
17. Witte R, Cannon M: Employee assistance programs: getting top management's support. *Personnel Administrator* 1979; 24:23-27
18. Jones KR, Vischi TR: Impact of Alcohol, Drug Abuse, and Mental Health Treatment on Medical Care Utilization: A Review of the Research Literature. *Med Care* 1979; 17(Dec suppl)
19. Busch EJ: Developing an employee assistance program. *Personnel J* 1981; 60:708-711
20. Ray JS: Having problems with worker performance? try an EAP. *Administrative Management* 1982; 43:17-49
21. Walsh DC: Employee assistance programs. *Milbank Mem Fund Q* 1982; 60:492-517
22. Ford RC, McLaughlin FS: Employee assistance programs: a descriptive survey of ASPA members. *Personnel Administrator* 1981; 26:29-35
23. Lewis KA: *Employee Assistance Programs: the State of the Art of Mental Health Services in Government and Industry: University Microfilms Number ADG81-24944*. Dissertation Abstracts International 1981; 42(A):2504
24. Hellan RT, Campbell WJ: Contracting for EAP services. *Personnel Administrator* 1981; 26:49-51
25. Gomez-Mejia LR, Balkin DB: Classifying work-related and personal problems of troubled employees. *Personnel Administrator* 1980; 25:27-32
26. Roman PM: From employee alcoholism to employee assistance: deemphasis on prevention and alcohol problems in work-based programs. *J Stud Alcohol* 1981; 42:244-272
27. Koranyi EK: Morbidity and rate of undiagnosed illnesses in a psychiatric clinic population. *Arch Gen Psychiatry* 1979; 36:414-419

NOW AVAILABLE!
THE 5 mL MULTI-DOSE VIAL

- ☐ same 50 mg/mL concentration
- ☐ cost-effective
- ☐ increased convenience

For the schizophrenic patient

**Sustained drug levels
with a single monthly dose**

HALDOL[®] DECANOATE
(HALOPERIDOL) INJECTION

**Sustained protection
from relapse**

Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL[®] (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

 **McNEIL
PHARMACEUTICAL**
McNEILAB, INC., Spring House, PA 19477

HALDOL DECANOATE (HALOPERIDOL) INJECTION

**Sustained protection
for the schizophrenic patient
with a single monthly dose**

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause

allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs—Abrupt discontinuation* of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia—As* with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia—Tardive dystonia*, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states* which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

7/20/88

**The Cambridge Examination for
Mental Disorders of the Elderly**
*Sir Martin Roth, F.A. Huppert, E. Tym and
C.Q. Mountjoy*

This package, consisting of complete interview and examination schedules, a booklet of test materials, score sheets, and a manual, comprises a standard assessment and diagnosis of senile dementia, including Alzheimer's disease and related mental disorders of the elderly.

1988/35161-8/Boxed Set \$95.00

**International Classification in
Psychiatry**

Unity and Diversity

*Edited by Juan E. Mezzich and Michael von
Cranach*

This book offers a comprehensive overview of psychiatric diagnosis and nosology. Fifty-two contributors, including representatives of twenty different countries, present historical roots, recent developments and current issues.

1988/432 pp./32754-7/Hardcover \$59.50

**An Introduction to Psychiatric
Research**

*Richard E. Gordon, Carolyn J. Hirsch and
Katherine K. Gordon*

Provides the tools necessary to demonstrate quantitatively to the public and to government, insurance, and accrediting agencies that their treatment is based on patients' needs, and is both appropriate and cost effective.

1988/257 pp./35094-8/Hardcover \$29.95

The Clinical Process in Psychiatry

Diagnosis and Management Planning

Barry Nurcombe and Rollin M. Gallagher

This book offers an important new perspective on the teaching of psychiatry by illuminating the process of thinking in clinical settings. It includes material on tactics and strategy in the clinical process, clinical procedures, diagnosis and planning, and a review of research on clinical reasoning.

1987/744 pp./24741-1/Hardcover \$75.00

28928-9/Paper \$32.50

Studies of Psychosocial Risk

The Power of Longitudinal Data

Edited by Michael Rutter

This new collection reflects the many conceptual and methodological advances that have taken place in the application of longitudinal research strategies, with particular reference to risk and protective factors in psychological risk.

1989/392 pp./35330-0/Hardcover \$59.50

Receptors and Ligands in Psychiatry

Edited by Amar K. Sen and Tyrone Lee

Intercellular and Intracellular Communication 3

1988/578 pp./30719-8/Hardcover \$120.00

**Receptors and Ligands in Neurological
Disorders**

Edited by Amar K. Sen and Tyrone Lee

Intercellular and Intracellular Communication 4

1988/319 pp./30720-1/Hardcover \$90.00

At bookstores or order from

Cambridge University Press

32 East 57th Street, New York, NY 10022.

Call toll-free: 800-872-7423, outside NY State: 800-227-0247, NY State only.

MasterCard & VISA accepted.

Where's the
best place
for a
patient
recovering
from a
drug or
alcohol
problem?...

Reprinted for the information of the readers of the American Journal of Psychiatry

THE BRITISH JOURNAL OF PSYCHIATRY

MARCH 1989

VOLUME 154

Annotation

- Monoamine oxidase inhibitors: rehabilitation from recent research? *D. Nutt and P. Glue* 287

Comment

- Neuronal misconnections and psychiatric disorder: is there a link? *R. Goodman* 292

Review Articles

- Day-hospital and community treatment for acute psychiatric illness: a critical appraisal. *F. Creed, D. Black and P. Anthony* 300
- Genetics, Alzheimer's disease and senile dementia. *D.W.K. Kay* 311
- Bipolar affective disorder: causes and prevention of relapse. *T. Silverstone and S. Romans-Clarkson* 321

Lecture

- The involvement of Soviet psychiatry in the persecution of dissenters. *A. Koryagin* 336

Papers

- Treatment of severe psychiatric illness in a day hospital. *F. Creed, P. Anthony, K. Godbert and P. Huxley* 341
- Lapse, relapse and survival among opiate addicts after treatment: a prospective follow-up study. *M. Gossop, L. Green, G. Phillips and B.P. Bradley* 348
- Circumstances surrounding the initial lapse to opiate use following detoxification. *B.P. Bradley, G. Phillips, L. Green and M. Gossop* 354
- Opiate withdrawal symptoms in response to 10-day and 21-day methadone withdrawal programmes. *M. Gossop, P. Griffiths, B. Bradley and J. Strang* 360
- Sex differences in the differentiation of psychiatric symptomatology. *M.E. Briscoe, J.L. Vázquez-Barquero, P. Williams, J.F. Díez-Manrique and C. Peña* 364
- Characteristics of psychiatric hospital absconders. *A.R. Tomison* 368
- Dexamethasone suppression test in dementia and depression: clinical and biological correlates. *J. Shrimankar, S.D. Soni and J. McMurray* 372
- PROQSY: a computerised technique for psychiatric case identification in general practice. *G. Wilkinson and A.C. Markus* 378
- The question of therapists' differential effectiveness: a Sheffield psychotherapy project addendum. *D.A. Shapiro, J. Firth-Cozens and W.B. Stiles* 383
- An uncontrolled study of cognitive therapy for morbid jealousy. *N.R. Bishay, N. Petersen and N. Tarrier* 386
- Life events and hostility in self-poisoning. *R. Farmer and F. Creed* 390
- Lithium prophylaxis and expressed emotion. *S. Priebe, C. Wildgrube and B. Müller-Oerlinghausen* 396
- Perceptivity and paraceptivity during measurement of gastric emptying in anorexia and bulimia nervosa. *P.H. Robinson* 400

The Current Literature

- Comments on the Northwick Park 'functional' psychosis study. *G. Goodwin, D.A.W. Johnson and R.G. McCreadie* 406

Correspondence

- A hundred years ago. *Researched by Henry Rollin* 410

Book Reviews

422

AUSTEN RIGGS CENTER



Psychoanalytic Psychotherapy in an
Open Hospital Setting

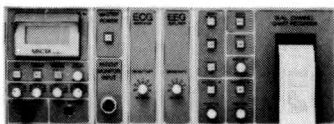
Treatment with Dignity, Personal
Responsibility and Quality Long-Term Results

The Austen Riggs Center
Stockbridge, Massachusetts 01262
(413) 298-5511

Founded in 1919

INTELLIGENT ECT FROM MECTA CORP. UL LISTED CSA CERTIFIED MODULAR AND COMPUTERIZED

SR-1



JR-1



FLEXIBILITY



PRINTED SELF TEST
AND TREATMENT RESULTS

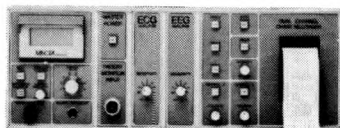
ADDITIONAL FEATURES INCLUDED WITH ALL SR MODELS ARE:

- EEG instrumentation amplifier
- Built-in 2 channel digital chart recorder
- Numeric timing marks during monitoring
- Printed record of energy level
- Printed date and time of treatment
- ECG instrumentation amplifier
- Selectable single or dual channel
- Printed record of treatment and self test
- Printed record of stimulus parameters
- Modular design for maximum flexibility

SR/JR FEATURES INCLUDE:

- Continuous reading of energy in Joules
- Tiltable Liquid Crystal Display
- Bi-polar brief pulse stimulus
- Adjustable constant current stimulus
- Audible warning prior to treatment
- Remote control capabilities
- 100% expected seizure induction
- Totally isolated for maximum safety
- Single or multiple energy control(s)
- All parameters displayed in text form
- Increased energy for difficult cases
- Built-in self test for patient safety
- Steady warning tone during treatment
- Protected STIMULUS CONTROL push button
- Timing accuracy better than .1%
- 1 year parts and labor warranty
- Operates on 120 or 240 VAC
- Complete with all accessories

SR-2



JR-2



SINGLE ENERGY
LEVEL CONTROLS

SIMPLICITY

MECTA Corporation 5622 SW Kelly Street Portland, OR 97201 (503) 245-6975

...on the job.

When your patient hesitates to enter a 28-day addiction treatment program because of family or job pressures, you now have an alternative. It's the CAREER™ program at Philadelphia Psychiatric Center.

CAREER is a *true* partial hospitalization program. Patients undergo two weeks of intensive 12-hour treatment days. Several more weeks of concentrated outpatient treatment follow—up to five evenings a week.

And, a special treatment feature lets your patient attend evening therapy sessions anytime he or she needs extra support. For a full year and at no cost.

When you admit a patient to CAREER, we consult with you to develop the optimum treatment plan, which can incorporate therapy sessions with you. We also provide timely progress updates.

The CAREER program works. Our patient recovery rate compares with full-time programs.

For more than 50 years, we've helped people return to normal, productive lives. CAREER continues that tradition.

For more information, please call at 215-473-8000.

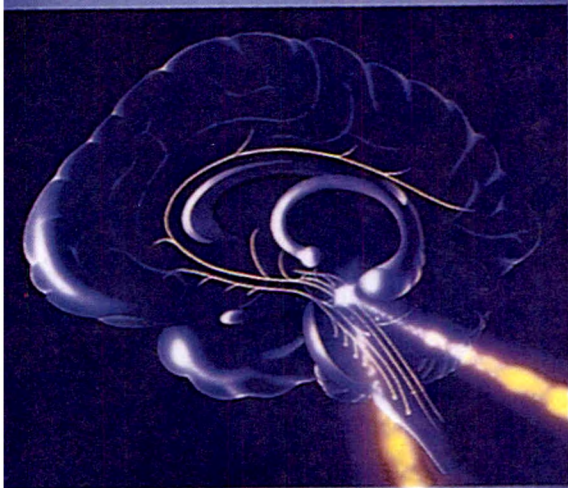
PHILADELPHIA
PSYCHIATRIC
CENTER



A subsidiary of Albert Einstein,
genius in healthcare.

© 1988 AEHF

The synapse—crossroads for serotonin



In depression

PROZAC[®]

fluoxetine hydrochloride

**a potent serotonin reuptake inhibitor...
represents a new class
of antidepressants.”¹**

Effectively relieves depression*

Unlike the tricyclics, Prozac specifically inhibits serotonin uptake. Its minimal action on other neurotransmitters may explain its favorable side-effect profile.

Fewer side effects to disrupt therapy

Side effects are generally mild and manageable, and include nausea, anxiety/nervousness, insomnia, and drowsiness

Avoid using MAO inhibitors concomitantly or in proximity to Prozac

Rash and/or urticaria occurred in 4% of clinical trial patients

A wide margin of safety

20-mg once-a-day therapy

PROZAC...
**A specifically different
antidepressant**



1. *Curr Ther Res* 1986;39:559-563.
*As defined by DSM-III.

*See adjacent page
for brief summary of
prescribing information.*

Prozac®

fluoxetine hydrochloride

Brief Summary: Consult the package literature for complete prescribing information.

Indications: Prozac is indicated for the treatment of depression.

Contraindications: Prozac is contraindicated in patients known to be hypersensitive to it.

Warnings: Monoamine Oxidase Inhibitors—Data on the effects of the combined use of fluoxetine and MAOI inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAOI inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered varioloid to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknown at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: General—Anxiety and insomnia—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 5% of patients treated with Prozac experienced anorexia. This incidence is approximately double that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo- and 3% of tricyclic-antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Life of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see Clinical Pharmacology and Dosage and Administration).

Use in Patients With Concomitant Illness—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Coagulation and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected. Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests—There are no specific laboratory tests recommended.

Drug Interactions—As with all drugs, the potential for interaction by a variety of mechanisms (i.e., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility (see Accumulation and Slow Elimination under Clinical Pharmacology).

Tryptophan—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors—See Warnings.

Other Antidepressants—There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (see Accumulation and Slow Elimination under Clinical Pharmacology).

Diazepam Clearance—The half-life of concurrently administered diazepam may be prolonged in some patients (see Accumulation and Slow Elimination under Clinical Pharmacology).

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Protein—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (see Accumulation and Slow Elimination under Clinical Pharmacology).

CNS-Active Drugs—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (see Accumulation and Slow Elimination under Clinical Pharmacology).

Epileptogenicity—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Cardiogenesis, Mutagenesis, Impairment of Fertility—There is no evidence of cardiogenic toxicity, mutagenicity, or impairment of fertility with Prozac. The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of cardiogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because a animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Use in Children—Safety and effectiveness in children have not been established.

Use in the Elderly—Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Hypotension—Several cases of hypotension (some with serum sodium lower than 110 mmol/L) have been reported. The hypotension appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Adverse Reactions: Commonly Observed—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The most common events causing discontinuation included: psychiatric (5.3%), nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

TABLE 1. TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event		Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Prozac (N=1,730)	Placebo (N=769)		Prozac (N=1,730)	Placebo (N=769)
Nervous			Body as a Whole		
Headache	20.3	15.5	Anxiety	4.4	1.9
Nervousness	14.9	9.3	Insomnia	3.4	3.1
Tremor	12.8	8.5	Depression	1.6	1.1
Drowsiness	11.8	6.5	Fatigue	1.4	—
Anxiety	9.4	5.5	Pain, chest	1.2	1.1
Typhoid	2.9	2.4	Alertness	1.2	1.1
Dizziness	2.7	3.3	Dyspnea	1.2	1.5
Fatigue	4.2	1.1	Respiratory		
Sedated	1.9	1.2	Upper		
Somatoform			respiratory		
disorders			infection	7.8	6.0
Somatoform	1.7	2.0	Flu-like		
disorders			syndrome	2.8	1.9
depressed	1.6	—	Pharyngitis	2.7	1.3
Urticaria	1.6	—	Rhinitis		
Lightheadedness	1.5	—	congestion	2.8	2.3
Concentration,			Headache		
decreased	1.5	—	sweat	2.3	1.8
Digestive			Stomatitis	2.1	2.0
Nausea	21.1	10.1	Cough	1.8	1.6
Diarrhea	22.3	7.0	Dyspepsia	1.4	—
dryness	9.5	6.0	Cardiovascular		
Anorexia	8.7	1.5	Hot flashes	1.8	1.0
Dyspepsia	8.4	4.3	Hypertension	1.3	1.4
Constipation	4.5	3.3	Musculoskeletal		
Pain			Pain, back	2.0	2.4
abdominal	3.4	2.9	Pain, joint	1.2	1.1
Vertigo	2.4	1.3	Pain, muscle	1.2	1.0
Stomach	1.8	—	Urogenital		
change	1.6	1.1	Urinary		
Retention	1.4	—	infection	1.2	—
Gastroenteritis	1.0	1.4	Special Senses		
Skin and			Visual		
Appendages			disturbance	2.8	1.8
Swelling,					
excessives	8.4	3.8			
Rash	2.7	1.8			
Pruritus	2.4	1.4			

*Events reported by at least 1% of Prozac-treated patients are included.
—Incidence less than 1%.

Incidence in Controlled Clinical Trials—Table 1 enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, users, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

Other Events Observed During the Premarketing Evaluation of Prozac—During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Unlabeled events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited at least one occasion while receiving Prozac. All reported events are included except those already listed in tabulations under COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole—Frequent: chills; Infrequent: chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; Rare: abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, myeloma, and serum sickness.

Cardiovascular System—Infrequent: angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; Rare: AV block (first-degree), bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System—Frequent: increased appetite; Infrequent: aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, and thirst; Rare: bloody diarrhea, cholelithiasis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hemoatemesis, hepatitis, hepatomegaly, hypercholesterolemia, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System—Infrequent: hypothyroidism; Rare: goiter and hyperthyroidism.

Hemic and Lymphatic System—Infrequent: anemia and lymphadenopathy; Rare: bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocytopenia.

Metabolic and Nutritional—Frequent: weight loss; Infrequent: generalized edema, hypoglycemia, peripheral edema, and weight gain; Rare: dehydration, gout, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypoglycemic reaction, hypokalemia, hypotension, and iron deficiency anemia.

Musculoskeletal System—Infrequent: arthritis, bone pain, bursitis, tenosynovitis, and twitching; Rare: bone necrosis, chondrocytopenia, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System—Frequent: abnormal dreams and agitation; Infrequent: abnormal gait, acute brain syndrome, ataxia, ataxia, amnesia, apathy, stasis, buccal-glossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperreflexia, hyposthesia, incoordination, libido increased, manic reaction, neuritis, neuropathy, parosmia reaction, psychosis, and vertigo; Rare: abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dyslexia, dyspyramidal syndrome, hyperreflexia, hysteria, myoclonus, myasthenia, parosmia, reflexes decreased, stupor, and torticollis.

Respiratory System—Frequent: bronchitis, rhinitis, and yawn; Infrequent: asthma, epistaxis, hiccup, hyperventilation, and pneumonia; Rare: apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/atelectasis, and pleural effusion.

Skin and Appendages—Infrequent: acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; Rare: eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, parosmia, purpura rash, pustular rash, seborrhea, skin discoloration, skin hypotrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses—Infrequent: amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; Rare: blepharitis, catarrh, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System—Infrequent: abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fluorocystitis, breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urinary impaction, and vaginitis; Rare: abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelocystitis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postmarketing Reports—Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after drug withdrawal, hyperproliferation, and thrombocytopenia.

Overdose: Human Experience—As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of meprobamate. Plasma concentrations of fluoxetine and meprobamate were 4.57 mg/L and 4.18 mg/L, respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; citalopram, 1.80 mg/L; meprobamate, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (see Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without sequelae.

PV 2472 DPP

1111788

Additional information available to the profession on request from



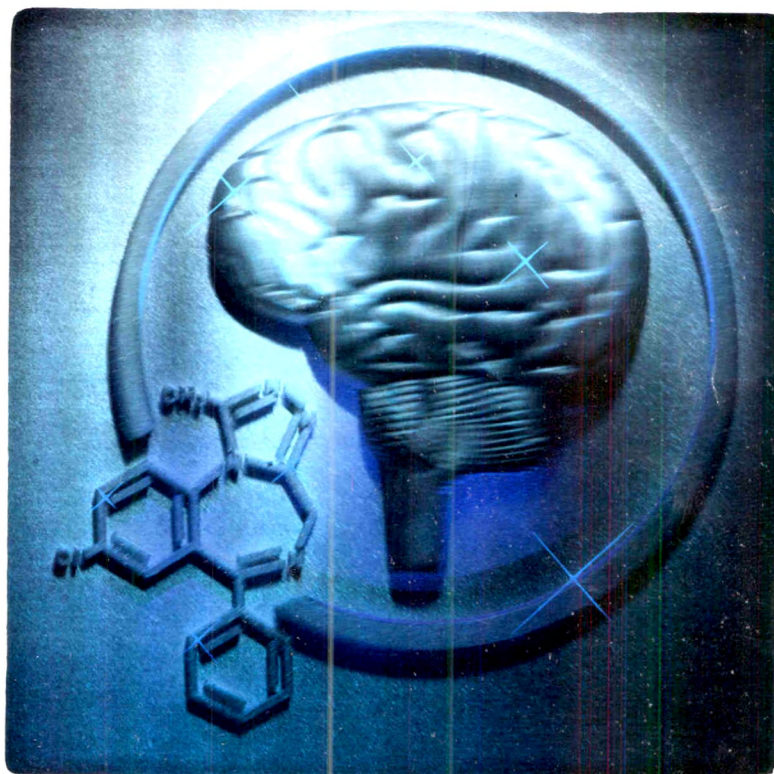
Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46285

Prozac® (fluoxetine hydrochloride, Dista)

Prozac® (fluoxetine hydrochloride, Dista)

Prozac® (fluoxetine hydrochloride, Dista)

XANAX ADDS A UNIQUE DIMENSION TO
YOUR PATIENT MANAGEMENT.



FOR ANXIETY ASSOCIATED
WITH DEPRESSION.

Xanax[®] 0.5 mg
Tablets
alprazolam[®]

Please see next page for brief summary of prescribing information

Upjohn

THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

© 1999 The Upjohn Company

XANAX ADDS A UNIQUE DIMENSION TO YOUR PATIENT MANAGEMENT.

XANAX® Tablets (alprazolam, C)

INDICATIONS AND USAGE

Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established. Periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS

XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women; hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation; thus reduce dose gradually (See Drug Abuse and Dependence and Dosage and Administration).

PRECAUTIONS

General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose (See Dosage and Administration). Hypomania and mania have been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs; (b) possible fetal abnormalities; (c) operating machinery or driving; (d) not increasing dose of the drug due to risk of dependence; (e) not stopping the drug abruptly. **Laboratory Tests:** Not ordinarily required in otherwise healthy patients. **Drug Interactions:** Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. **Drug/Laboratory Test Interactions:** No consistent pattern for a drug or test. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No carcinogenic potential or impairment of fertility in rats. **Pregnancy:** See Warnings. **Nonteratogenic Effects:** The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. **Labor and Delivery:** No established use. **Nursing Mothers:** Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. **Pediatric Use:** Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX,

e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. **Gastrointestinal:** Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. **Cardiovascular:** Tachycardia/palpitations, and hypotension. **Sensory:** Blurred vision. **Musculoskeletal:** Rigidity and tremor. **Cutaneous:** Dermatitis/allergy. **Other side effects:** Nasal congestion, weight gain and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation (See Warnings).

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

Liver enzyme elevations, gynecostasia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. **Controlled Substance Class:** XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION

Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED

XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

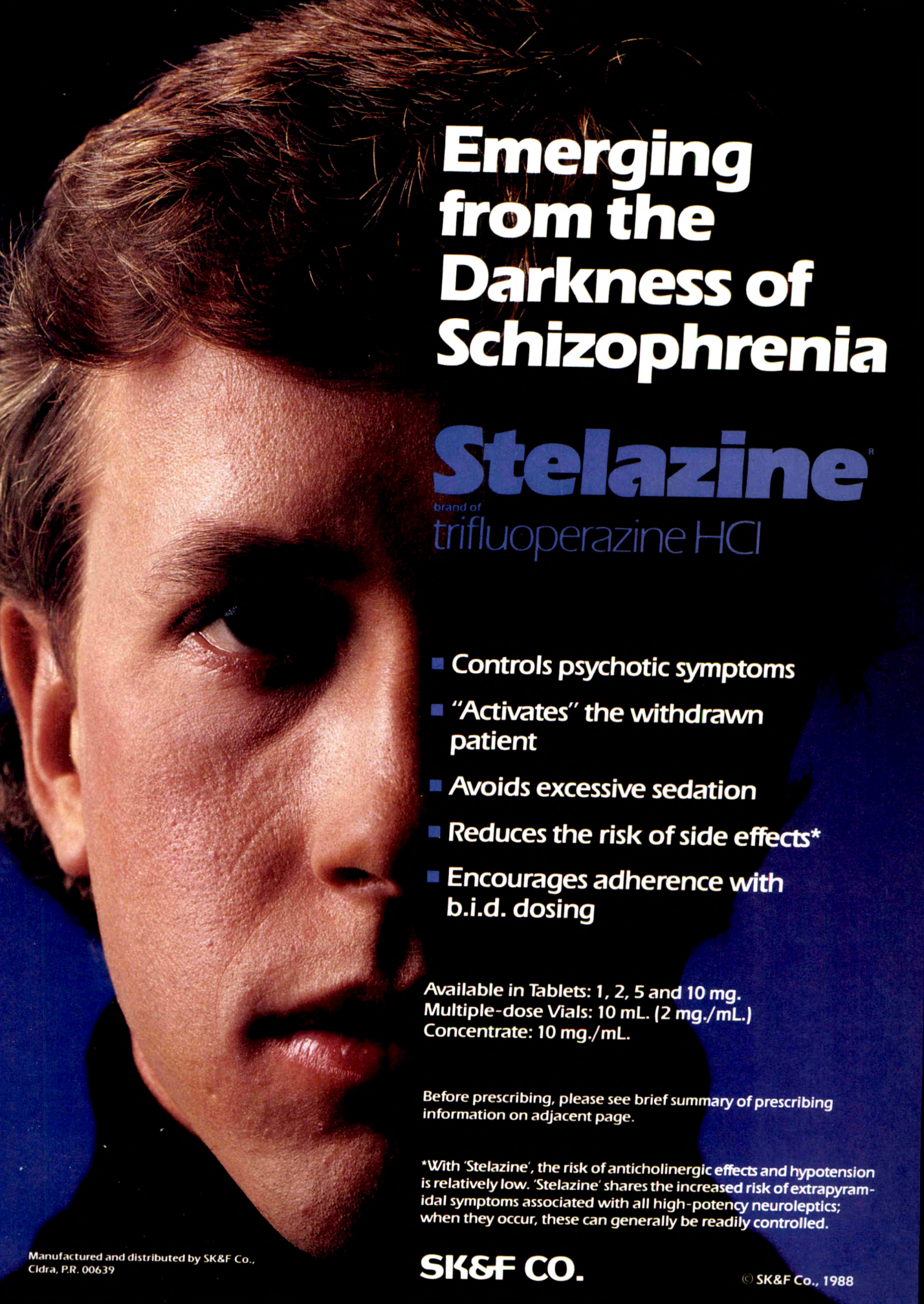
CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

Upjohn

THE UPIJOHN COMPANY
Kalamazoo, Michigan 49001 USA

B-8-S
J-9191
January, 1989

Xanax® 0.5 mg
Tablets
alprazolam®



Emerging from the Darkness of Schizophrenia

Stelazine[®]
brand of
trifluoperazine HCl

- Controls psychotic symptoms
- "Activates" the withdrawn patient
- Avoids excessive sedation
- Reduces the risk of side effects*
- Encourages adherence with b.i.d. dosing

Available in Tablets: 1, 2, 5 and 10 mg.
Multiple-dose Vials: 10 mL (2 mg./mL.)
Concentrate: 10 mg./mL.

Before prescribing, please see brief summary of prescribing information on adjacent page.

*With 'Stelazine', the risk of anticholinergic effects and hypotension is relatively low. 'Stelazine' shares the increased risk of extrapyramidal symptoms associated with all high-potency neuroleptics; when they occur, these can generally be readily controlled.

Manufactured and distributed by SK&F Co.,
Cidra, P.R. 00639

SK&F CO.

© SK&F Co., 1988

Stelazine®

brand of
trifluoperazine HCl

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. [See PRECAUTIONS.]

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If renal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance. If neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuroleptic (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dyskinesia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy; and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

SK&F CO.

Manufactured and distributed by
SK&F Co., Cidra, P.R. 00639

BRS-SZL63

© SK&F Co., 1988

Consultation Service

American Psychiatric Association

Administrative, Organizational, Programmatic, and Quality of Care Consultation to:

- Psychiatric units in general hospitals
- Outpatient clinics
- Private and state psychiatric hospitals
- Specialized hospitals
- Residential programs
- Community mental health centers
- State mental health systems
- Specialized services for:
 - mentally ill persons
 - mentally retarded and developmentally disabled persons
 - children and adolescents
 - the aging
 - drug abusers
 - alcohol abusers
 - criminal offenders

Our Range of Services Includes but Is Not Limited to:

- conflict resolution
- design and planning of clinical programs
- analysis of clinical and management systems
- integration of services, to provide continuity of care
- evaluation of clinical services
- assistance in developing priorities among service needs
- advice on moving toward compliance with standards of government or private accreditation boards
- aid in meeting the requirements of external planning bodies
- referral to other sources of help
- planning to meet future service needs, consistent with fiscal contingencies

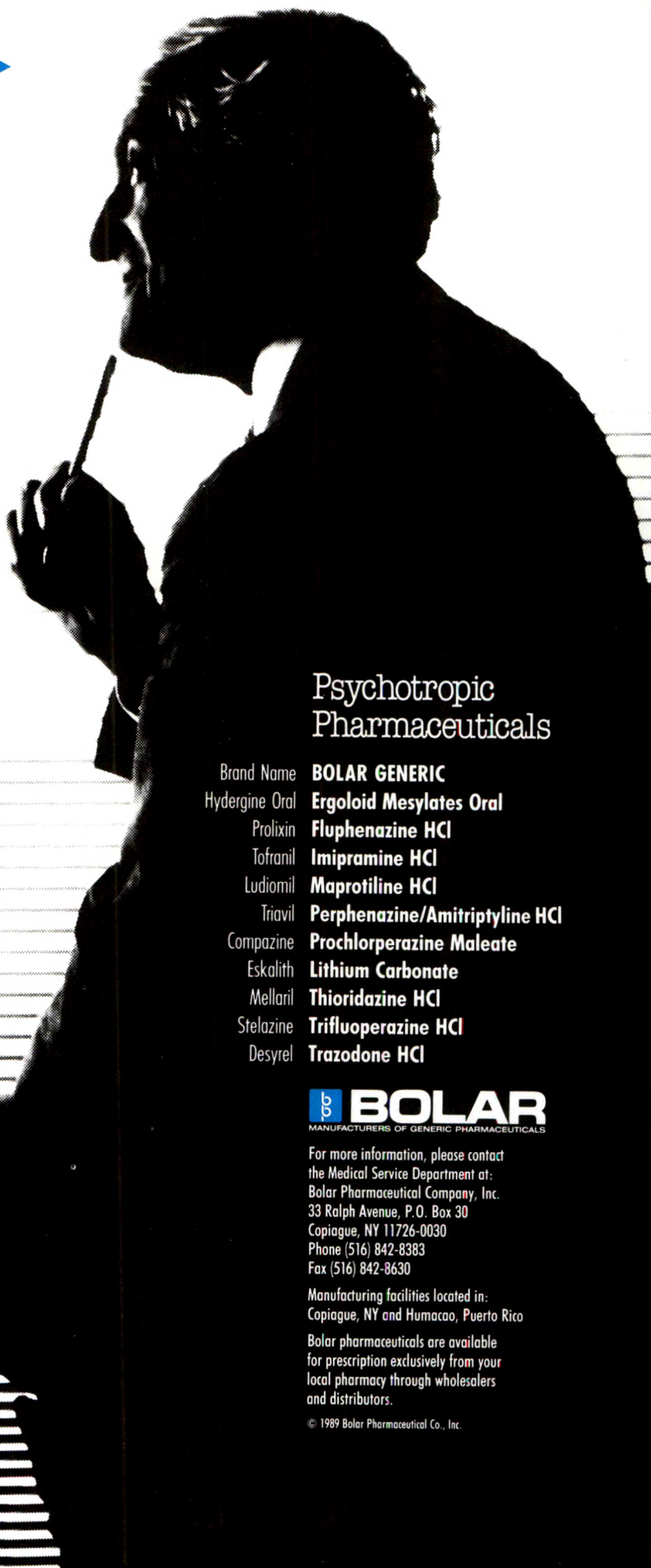
CONTACT:

Consultation Service
American Psychiatric Association
1400 K Street, N.W.
Washington, D.C. 20005
(202) 682-6173

My patient deserves ►
a choice when it
comes to prescription
pharmaceuticals.



I'm grateful that
my psychiatrist provided
me with generic
alternatives.



Psychotropic Pharmaceuticals

Brand Name	BOLAR GENERIC
Hydergine Oral	Ergoloid Mesylates Oral
Prolixin	Fluphenazine HCl
Tofranil	Imipramine HCl
Ludiomil	Maprotiline HCl
Triavil	Perphenazine/Amitriptyline HCl
Compazine	Prochlorperazine Maleate
Eskalith	Lithium Carbonate
Mellaril	Thioridazine HCl
Stelazine	Trifluoperazine HCl
Desyrel	Trazodone HCl



For more information, please contact
the Medical Service Department at:
Bolar Pharmaceutical Company, Inc.
33 Ralph Avenue, P.O. Box 30
Copiague, NY 11726-0030
Phone (516) 842-8383
Fax (516) 842-8630

Manufacturing facilities located in:
Copiague, NY and Humacao, Puerto Rico

Bolar pharmaceuticals are available
for prescription exclusively from your
local pharmacy through wholesalers
and distributors.

© 1989 Bolar Pharmaceutical Co., Inc.



Emergency medicine.

Management of severely disruptive behavior: Ativan® Injection with a neuroleptic.

Rapid tranquilization with a wider margin of safety.

Although neuroleptic agents provide an effective means of controlling violent or destructive behavior, their use is associated with a risk of serious and potentially irreversible adverse effects.¹⁻² Dose reduction is the best way to minimize this risk, but such a solution may not be possible during an emergency. The use of ATIVAN Injection combined with a low-dose neuroleptic provides an alternative pharmacologic approach for sedating anxious and agitated patients exhibiting severely disruptive behavior.

Clinical experience with this combination suggests that effective

control can be achieved with lower neuroleptic doses than when using a neuroleptic alone.³

Ativan® Injection: Pharmacologically desirable as an adjunct for sedation.

Unlike other benzodiazepines, ATIVAN Injection is readily absorbed following intramuscular administration,⁴ with peak plasma concentrations occurring in approximately 60 to 90 minutes.⁵ Mean half-life is about 16 hours and the desired sedative and anxiolytic effects usually last 6 to 8 hours.^{5*}

*The additive central-nervous system effects of neuroleptics should be borne in mind when used concomitantly with ATIVAN Injection.

Please see the adjacent page for a brief summary of prescribing information.

Ativan® Injection I.M. (lorazepam)

**Calm the patient,
curtail adverse reactions.**

ATIVAN® INJECTION I.M. (LORAZEPAM) ©

DESCRIPTION: Ativan® (lorazepam) Injection, a benzodiazepine with anxiolytic and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(α -chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative. **CLINICAL PHARMACOLOGY:** IV or IM administration of recommended dose of 2 to 4 mg lorazepam Injection in adult patients is followed by dose-related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus acted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as demonstrated under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15 to 20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam Injection usually last 6 to 8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers revealed that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse (See WARNINGS and ADVERSE REACTIONS).

Clinically employed doses of lorazepam Injection do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8 to 10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam Injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults — for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious and/or about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation (See WARNINGS).

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE, IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam Injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide) is renal, lorazepam is not recommended in hepatic and/or renal failure. This does not preclude its use in patients with mild to moderate hepatic or renal disease. Where injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of edema of eye, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucinations and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlorazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam Injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam Injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam Injection is used for pre-anesthetic procedures, therefore a separate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g., phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concurrently with or during period of recovery from lorazepam Injection (See CLINICAL PHARMACOLOGY and WARNINGS). Use extreme care in giving lorazepam Injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible hypoventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE AND ADMINISTRATION). When lorazepam is used IV as premedication prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concurrently with the recommended dose (See ADVERSE REACTIONS).

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g., sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam Injection as premedication that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam Injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam Injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam Injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials, no laboratory test abnormalities were identified with single or multiple doses of lorazepam Injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total protein.

Drug Interactions: Lorazepam Injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concurrently with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g., narcotic analgesics, inhalation anesthetics, scopolamine, atropine and various tranquilizing agents.

Cardiogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam Injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE AND ADMINISTRATION). On rare occasions (3/1580), patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedication). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately postinjection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary under-ventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam Injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over a prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypoxia, stages one to three coma and, very rarely, death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. While normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg of physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedication, usual IM doses of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedications, individualize dose (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS). Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS). For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure. Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients to whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses — as high as 0.05 mg/kg up to total of 4 mg — may be given (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS). Doses of other injectable CNS depressants should ordinarily be reduced (See PRECAUTIONS). For optimum effect, measured as lack of recall, IV lorazepam should be administered 15 to 20 minutes before anticipated operative procedure.

EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (See WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam Injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam Injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam Injection is compatible for dilution purposes with Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan® (Lorazepam) Injection, Wyeth, is available in single- and multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 1 ml and 10 ml vials and 1 ml fill to 2 ml TUBEX.
4 mg/ml, NDC 0008-0570; 1 ml and 10 ml vials and 1 ml fill to 2 ml TUBEX.

For IM or IV Injection. Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX — (1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial — Aspirate desired amount of lorazepam Injection into syringe. Then proceed as described under TUBEX.

CI 3261-2 6/22/83

References:

- Graham R, Glinther W, Ruther E: Adverse effects of psychotropic drugs. In Hippius H, Winokur G (eds): *Clinical Psychopharmacology*. Amsterdam: Excerpta Medica, 1983, pp 378-385.
- Dubin WR: Rapid tranquilization: Antipsychotics or benzodiazepines? *J Clin Psychiatry* 1988;49(suppl):5-11.
- Sakzuan C, Green M, Rodriguez-Vila F, et al: Benzodiazepines combined with neuroleptics for management of severe disruptive behavior. *Psychosomatics* 1986;27(suppl):17-21.
- Harvey SC: Hypnotics and sedatives. In Gilman AG, Goodman LS, Rail TW, et al (eds): *The Pharmacological Basis of Therapeutics*, ed 7. New York: Macmillan Publishing Company, 1985, pp 339-371.
- Data on file, Wyeth-Ayerst Laboratories.

**WYETH-AYERST
LABORATORIES**
Philadelphia, PA 19101

© 1989, Wyeth-Ayerst Laboratories

When so much depends on you . . .

THE CHILDREN'S CAMPUS

- A comprehensive residential treatment center providing a true continuum of care. **The Children's Campus** has been serving troubled children and adolescents for over 100 years
- **The Children's Campus** is designed to be more than a single focused residential facility. The Children's Campus utilizes a "Continuum of Treatment" based upon realistic expectations and needs.
- **The Children's Campus** offers a start-to-finish approach utilizing individualized applications of a variety of established treatment components, supported by a structured positive living environment.
- The fundamental goal of all **The Children's Campus** interventions is to enable the child to work through life issues and emerge as an individual with a healthy self-concept, a strong value system, and the ability to make appropriate and responsible choices.
- The "Continuum of Treatment" offered by **The Children's Campus** allows the child to move from a more restrictive environment when appropriate to a less restrictive environment, avoiding the trauma of a new setting, new treatment, and new faces.
- **The Children's Campus** is located in beautiful North Central Indiana only a few hours away from Chicago, Indianapolis, Detroit, and Cleveland. The Children's Campus is only ten minutes from the University of Notre Dame.

For more information, call or write:

Admissions Coordinator
The Children's Campus
1411 Lincoln Way West
Mishawaka, IN 46544-1690
(219) 259-5666

Third Party reimbursement accepted



CMA



**PSYCHIATRIC &
PSYCHOLOGICAL SERVICES**

**DIAGNOSTIC AND
EVALUATION SERVICES**

**PREFERRED ADOLESCENT
CARE CENTER**

SEXUAL ABUSE TREATMENT

**SUBSTANCE ABUSE
TREATMENT**

ON-GROUNDS SCHOOL

TREATMENT GROUP HOMES

TREATMENT FOSTER HOMES

INDEPENDENT LIVING

PREGNANCY PROGRAM

**MOTHER/INFANT BONDING
PROGRAM**

FAMILY SUPPORT PROGRAM

THE BEST CANDIDATE FOR YOUR POSITION OPENING MAY BE ONE OF H&CP'S 24,000 READERS

PSYCHIATRISTS

PSYCHOLOGISTS

NURSES

ADMINISTRATORS

SOCIAL WORKERS

PHARMACISTS

EDUCATORS

They all read H&CP!



As the field's only monthly interdisciplinary journal, *H&CP* is the one place you can advertise each and every professional staff vacancy that arises within your treatment facility.

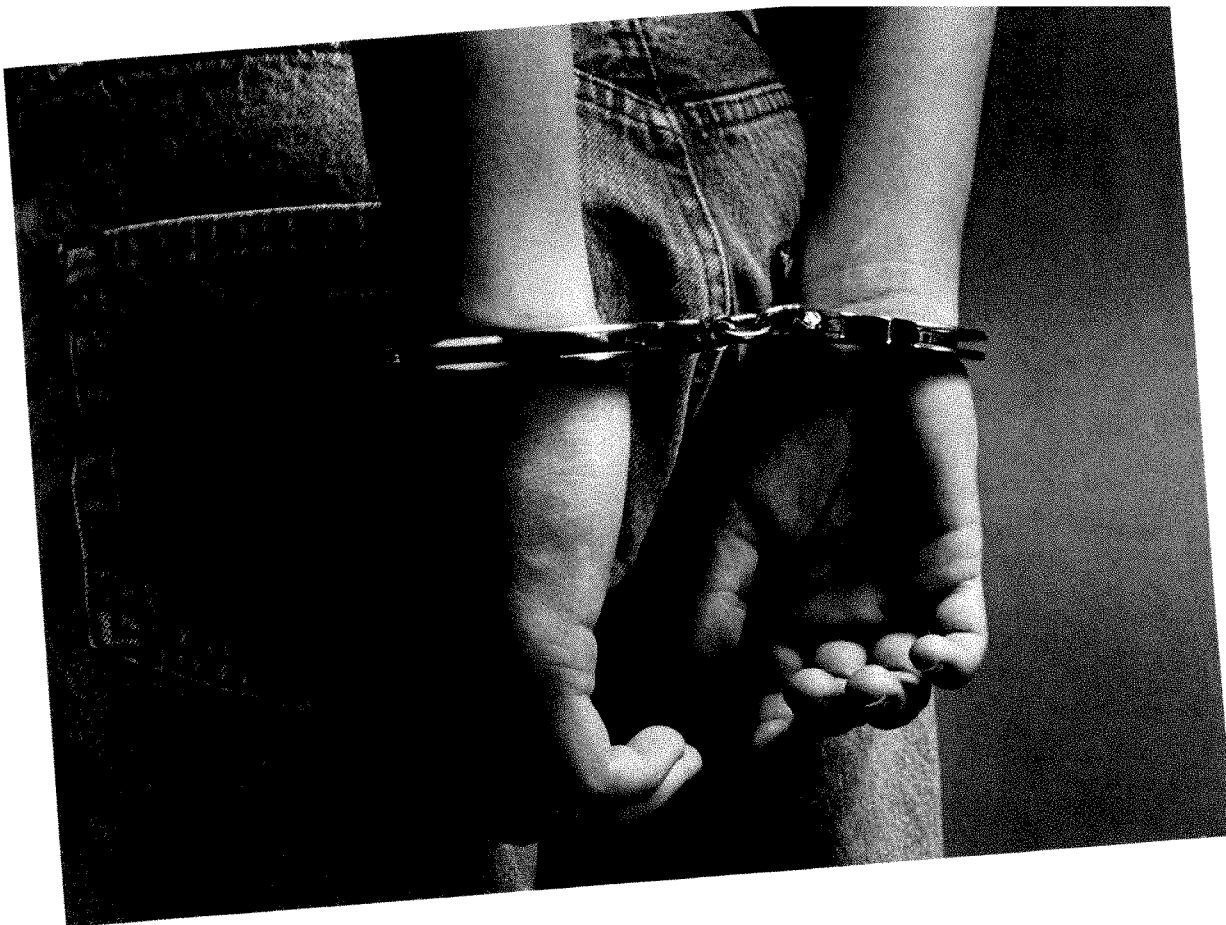
No other primary journal offers such a diversified professional audience and provides such an efficient medium for spreading your advertising message to the mental health professionals you want to reach.

And *H&CP*'s advertising rates are reasonable, too.

Why don't you let *H&CP* work for you?

For more information call Joanie Lefkowitz at (202) 682-6124.

H&CP Advertising
American Psychiatric Association
1400 K Street, N.W.
Washington, D.C. 20005



Rx FOR CONDUCT DISORDERS

If you're treating a conduct-disordered adolescent male who doesn't respond to outpatient psychotherapeutic intervention, it may be time to suggest a regimen of 24-hour structure and treatment.

At St. Francis we have specialized in the treatment of these disorders for 40 years. We offer individual, group, and milieu therapy with adjunctive remedial, occupational, activity, and family therapies in a one-on-one therapeutic setting. Patients are mainstreamed in local community schools and participate in community activities.

Our three residential treatment centers in New York and Kansas are limited to a maximum of twenty-six boys in grades seven through twelve. An individualized treatment plan is developed for each resident by the professional staff working together with the child, his parents or guardian, and those who have referred him to us.

Based on more than two decades of follow-up research, over two-thirds of the young men resolve their problems and continue to lead healthy, normal, and productive lives five years after their release.

We work closely with each boy's psychiatrist to chart new directions that can last a lifetime — after an average stay of just one year. Call for a free consultation to determine if the St. Francis Homes can complement the care you're providing.

St. Francis is accredited by the Joint Commission on Accreditation of Healthcare Organizations and certified for CHAMPUS payment.



For information and referral, contact:
 Richard W. Burnett, ACSW
 Box 1340
 Salina, Kansas 67402-1340
 Call Toll Free — 1-800-423-1342
 In New York — 1-800-822-4363
 In Kansas — 913-825-0541 Collect

Ellsworth, KS • Salina, KS • Lake Placid, NY • JCAHO Accredited • CHAMPUS Certified

© 1988 St. Francis 240

When Psychotic Features Complicate Depression, Simplify the Treatment With ASENDIN

A single agent for depression with psychotic features

"Amoxapine...is a weak blocker of dopamine receptors *in vivo* and *in vitro*. Such a drug might be especially useful in the treatment of psychotic depressions."¹ Elliott Richelson, MD *Journal of Clinical Psychiatry*, 1982

On the Brief Psychiatric Rating Scale, treatment with ASENDIN improved the condition of 86% of depressed patients with psychotic features.²

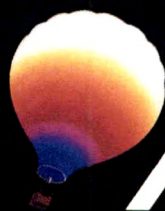
Single-blind study by Raymond F. Anton, MD, et al *Journal of Clinical Psychiatry Monograph*, 1986

A simple, easy-to-follow dosage schedule for depression with psychotic features

Suggested dosage in depression with psychotic features 100 mg bid. Adjust according to the clinical response and tolerance.*

*ASENDIN may be given in a single daily dose, not to exceed 300 mg, preferably at bedtime. If the total daily dosage exceeds 300 mg, it should be given in divided doses.

ASENDIN inhibits reuptake of norepinephrine and serotonin and also has dopamine-blocking activity which may be associated with neuroleptic side effects, including tardive dyskinesia, in some patients. Please see brief summary of prescribing information, on adjacent page, especially **Warnings** and **Information for the Patient** sections.



ASENDIN[®]
amoxapine

ASPIRIN® acetylsalicylic Tablets
25 mg, 50 mg, 100 mg, 180 mg

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. *In vitro* tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Warnings: Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders. **INDICATIONS:** ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation. **CONTRAINDICATIONS:** Prior hypersensitivity to tetracycline compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hypertensive crisis, severe convulsions, and deaths have occurred in patients receiving both antidepressants and monoamine oxidase inhibitors simultaneously. Before ASENDIN is given to patients on MAO inhibitors, a minimum of 14 days to elapse, then initiate cautiously, with careful prompt to monitor until patients are adequately stabilized.

WARNING: tardive dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dysrhythmic movements, may develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amisapip is not an antipsychotic, but it has substantial neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of laryngeal dystonia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatology suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be assessed periodically.

If signs and symptoms of lardose dykinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

Anticholinergic Syndrome: Anticholinergic syndrome is a clinical entity caused by inhibition of acetylcholine release from autonomic cholinergic neurons. NMS has been reported in association with anticholinergic drugs. Clinical manifestations are hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Clonidine is complicated. Rule out serious medical illness (eg, pneumonia, systemic infection) and inadequately treated endocrinopathies (diabetes mellitus). Other considerations in differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology. Management of NMS includes immediate discontinuation of anticholinergic and other drugs essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of complications. Treatment of severe cases may require mechanical ventilation, cooling, and plasmapheresis. The prognosis is generally good, although some patients may have persistent sequelae. Anticholinergic toxicity can be fatal if untreated.

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Other antidepressants may also be contraindicated with history of acute glaucoma or those with recent or latent depressive disorders.

PRECAUTIONS: *General:* Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring

reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause an "anxious" or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. AMENDIN amaranthine should be discontinued if rash and/or fever develop. Amaranthine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in

<1% of patients. Rarely, symptoms indicative of lardive dyskinesia have been reported. Information for the patient: It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of lardive dyskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired. Drug Interactions: See CONTRAINDICATIONS regarding concurrent use of in-

cyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interactions with other drugs have not been studied.

studies have not been done, and the possibility should be considered. Therapeutic interactions: Concurrent administration with electroshock may increase hazards associated with such therapy. Carcinogenesis, impairment of fertility: In a 21-month toxicity study of three-dose levels in rats, peritoneal histiocytic sarcoma occurred with slightly increased incidence at doses of 30 times the human dose. Gonadal and embryofetal toxicity reported in low incidence at 10 and mid-dose levels.

dence of doses 5-10 times the human dose. Pancreatic adenocarcinoma was observed in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length.

Pregnancy, Pregnancy Category C: Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASBENDOL. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the

human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing mothers: ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women. Pediatric use: Safety and effectiveness in children below the age of 16 have not

ADVERSE REACTIONS: Reported in Controlled Studies: incidence greater than 1%—Most frequent were sedative and anticholinergic—drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).
Less frequently reported symptoms were: PMS and nervous disorder, anxiety, insomnia, restlessness, nervousness, painless

Less frequently reported reactions were: CNS and neuromuscular—drowsiness, irritability, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, static discharges in EEG patterns. Allergic—edema, skin rash. Endocrine—elevation of prolactin levels. Gastrointestinal—nausea. Other—dizziness, headache, italgias, weakness, excessive appetite, increased perspiration. Incidence less than 1%. **Anti-histaminic**—disturbances of accommodation, mydriasis, delayed micturition, blurred vision. **Anticholinergic**—disturbances of accommodation, mydriasis, delayed micturition, blurred vision. **Antidysrhythmic**—disturbances of accommodation, mydriasis, delayed micturition, blurred vision. **Antidysrhythmic**—disturbances of accommodation, mydriasis, delayed micturition, blurred vision.

slion, urinary retention, nasal stuffiness. Cardiovascular—hypotension, hypertension, syncope, tachycardia. Allergic—drug fever, urticaria, photoensitization, pruritus, rare vasculitis, hepatitis. CNS and neuromuscular—tingling, paresthesias of the extremities, tinnitus, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, serapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported. (See

WARNINGS: Hematologic—leukopenia, agranulocytosis. Gastrointestinal—epigastric distress, vomiting, flatulence, abdominal pain, peptic ulcers, diarrhea. Endocrine—increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion. Other—loss of appetite, weight gain or loss, altered liver function, painful ejaculation. Drug relationship unknown: Reported rarely, but under circum-

stances where drug relationship was unknown: Anticholinergic—paralytic ileus. Cardiovascular—atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block. CNS and neuromuscular—hallucinations. Hematologic—thrombocytopenia, eosinophilia, purpura, petechiae. *†*Astrocidalind—parotid swelling. Endocrine—change in blood glucose levels. Other—paronychia, hepatitis, jaundice, urinary frequency, inguinal swelling, anemia, alopecia.

Additional adverse reactions reported with other antidepressant drugs: Anticholinergic—sublingual adenitis, dilation of the urinary tract. CNS and neuromuscular—delirium. Gastrointestinal—dysphagia, black tongue. Endocrine—gynecomastia. OVERDOSE: Signs and symptoms

serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and ataxia are other serious complications of subdural ALENDRON overdose.

age in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures.

Treatment
Treatment of AEDIDN overdosage should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that

Convolutions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for nondrug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG

typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdose with this drug. Fatality and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENIDIN overdose patients.

1. Richelson E: Pharmacology of antidepressants in use in the United States. *J Clin Psychiatry* 1982;43:4-11.
2. Anton RE, Hibi A, Diamond BL, et al: Amoxapine treatment of psychotic depression: dose effect and dopamine blockade. *J Clin Psychiatry Monograph* 1986;4:32-36.

 LEDERLE LABORATORIES
A Division of American Cyanamid Company
Wayne, NJ 07470

● 1988 Ledinger Laboratories 6613

Page 4/28

663-2

APA Circulation Department,
AMERICAN PSYCHIATRIC ASSOCIATION
1400 K Street, N.W.
Washington, D.C. 20005

THE AMERICAN JOURNAL OF PSYCHIATRY

Information for Contributors

GENERAL POLICIES

Manuscripts are accepted for consideration by the *American Journal of Psychiatry* with the understanding that they represent original material, have not been published previously, are not being considered for publication elsewhere, and have been approved by each author. Authors submitting manuscripts containing data or clinical observations already used in published papers or used in papers that are in press, submitted for publication, or to be submitted shortly should provide information on those papers to the Editor.

The requirements stated below are in accordance with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

Copyright Transfer and Submission Approval

The *Journal* requires approval of manuscript submission by all authors in addition to transfer of copyright to the American Psychiatric Association so that the author(s) and the Association are protected from misuse of copyrighted material. A submission approval and copyright transfer form will be forwarded to authors along with a letter acknowledging receipt of their manuscript. Manuscripts will not receive a final decision until a completed form has been received in the editorial office.

In addition, authors must obtain letters of permission from publishers for use of extensive quotations (more than 500 words). The *Journal* does not publish tables or figures that have appeared in another English-language publication.

Disclosure of Commercial Interests

All forms of support, including drug company support, must be acknowledged in the author's footnote (see "Acknowledgments" under the Title Page section). Also, authors must disclose in their cover letter any commercial or financial involvements that might present an appearance of a conflict of interest in connection with the submitted article, including (but not limited to) institutional or corporate affiliations not already specified in the author's footnote, paid consultancies, stock ownership or other equity interests, and patent ownership. This information will be kept confidential and will not be shared with the reviewers. Such involvements will not be grounds for automatic rejection of the manuscript. Should the article be accepted for publication, the Editor and the authors will consult on whether, and to what extent, this information should be included in the published article.

Patient Anonymity

Ethical as well as legal considerations require careful attention to the protection of a patient's anonymity in case

reports and elsewhere. Identifying information such as names, initials, hospital numbers, and dates must be avoided. In addition, authors should disguise identifying information when discussing the characteristics and personal history of patients.

Informed Consent

Manuscripts that report the results of experimental investigation with human subjects must include a statement that informed consent was obtained after the procedure(s) had been fully explained. In the case of children, authors are asked to include information about whether the child's assent was obtained.

Review Process

All papers are reviewed to determine the originality, validity, and importance of content and conclusions. In addition to the regular review process, peer review for statistical content may be required for some manuscripts. This will be determined by the *Journal's* Statistical Editors. Authors will be sent reviewer comments that are judged to be useful to them. All reviewers remain anonymous. Once the Editor has made a final decision on a paper, the authors of that paper will be informed.

SUBMISSION OF MANUSCRIPTS

The original manuscript and three copies should be submitted to John C. Nemiah, M.D., Editor, *American Journal of Psychiatry*, 1400 K St., N.W., Washington, DC 20005. All correspondence will be sent to the first-named author unless otherwise specified. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the *Journal* it is being submitted (i.e., Special Article, Regular Article, Brief Communication, or Clinical and Research Report); papers will only be reviewed after such a statement has been received from the author.

Authors will be notified of the receipt of their paper and the number assigned to it. **This number must be included in all further correspondence.** It is imperative that the corresponding author of submitted papers notify the *Journal* of changes of address. Because of escalating postage costs, no manuscripts submitted to the *Journal* will be returned to authors except upon special request. Authors must make this request in their original submission letter and include a self-addressed, postage-paid envelope.

Single Case Reports

Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. All single case reports will be peer reviewed. Reports of successfully treated patients should include data on the number of patients treated unsuccessfully by the same method, with an indication of the temporal order of the successes and failures.

Annual Meeting Papers

Authors may submit their papers before the annual meeting, but such papers cannot be published until after the meeting. All papers must be accompanied by a statement that they are in final form. These papers are subject to the same peer review as other papers and must conform to the requirements for one of the types of articles specified in the next section.

TYPES OF ARTICLES

Special Articles

These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including an abstract of no more than 100 words, tables, and figures) and may not include more than 100 references.

Regular Articles and Brief Communications

The only difference between these two types of papers is length. **Regular Articles** contain no more than 3,800 words, including an abstract of no more than 100 words, references, tables, and figures. **Brief Communications** contain no more than 2,500 words, including an abstract of no more than 100 words, references, tables, and figures. (A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words.) Articles that exceed 3,800 words will be returned unreviewed to the authors.

Clinical and Research Reports

A prompt publication policy (i.e., publication within 4 to 6 months after acceptance) is in effect for Clinical and Research Reports. Manuscripts may contain no more than one table and a maximum of 10 references; figures may not be used. Papers may contain a **maximum** of 1,300 words, including an abstract of no more than 40 words, text, references, and an optional table (estimate 15 words per reference, 100 words for a double-spaced table that fills one-half of a vertical page, and 150 words for a double-spaced table that fills one-half of a horizontal page). These articles present 1) new research findings, 2) data from pilot studies, 3) worthwhile replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

Other Sections

Letters to the Editor. Brief letters (maximum of 500 words and 5 references; no tables or figures) will be considered if they include the notation "for publication." The number of words should appear in the upper right corner. Letters critical of an article published in the *Journal* will automatically be sent to the authors for reply. Because of space limitations, not all letters can be printed. The *Journal* will notify authors about the disposition of their letters but does not return those that are not published. A letter must be signed by all of its authors. All letters will be edited; edited letters will not be sent to authors for approval. Letters must be typed double-spaced throughout on 8½×11 inch paper; three copies are required. Letters that do not meet these specifications will be returned for revision. Reprints are not available. **Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. Case reports submitted as Letters to the Editor will be peer reviewed.**

Book Forum. Books for review may be sent to the Book Forum Editor, Nancy C. Andreasen, M.D., Ph.D., University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242. Book reviews are usually solicited by the Book Forum Editor. Authors interested in reviewing a particular book should communicate directly with Dr. Andreasen. Reprints of reviews are not available.

TYPING AND ARRANGING THE PAPER

All parts of the manuscript, including case reports, quotations, references, and tables, must be **double-spaced** throughout. Manuscripts must be typed in upper- and lowercase on one side only of 8½×11 inch **nonerasable** bond paper. All four margins must be 1½ inches. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) references, and 5) tables and/or figures. All pages must be numbered.

STYLE SPECIFICATIONS

Title Page

The number of words, tables, and figures in the paper and the telephone number of the corresponding author should be typed in the upper right-hand corner of the title page. At least three key words that describe the content of the paper should be typed in the lower right corner of the page.

Title. The title should be informative and as brief as possible. Two-part titles should be avoided.

By-line. Authors listed in the by-line should be limited to principal researchers and/or writers; collaborators may be acknowledged in a footnote. Authors' first names are preferred to initials. Degrees should be included after each author's name.

Previous presentation. If the paper has been presented at a meeting, please give the name of the meeting, the place, and the inclusive dates.

Location of work and address for reprints. Provide the department, institution, city, and state **where the work was done**. Include a full address for the author who is to receive reprint requests.

Acknowledgments. Grant support should be acknowledged in a separate paragraph and should include the full name of the granting agency and grant number. The *Journal*

does not allow acknowledgment of persons involved with the preparation or typing of manuscripts. Acknowledgment of individuals involved with the scientific content of the work should not exceed four typed lines. Drug company support of any kind must be acknowledged.

Abstract

The abstract is a single paragraph no longer than 100 words for Special Articles, Regular Articles, and Brief Communications and no longer than 40 words for Clinical and Research Reports. Authors should use the active voice and the third person.

Text

Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

Research design and statistics. The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. All significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ($F=4.32$, $df=3$, 17 , $p<0.05$).\" Reviewers will evaluate the appropriateness of the analyses.

Abbreviations. Spell out all abbreviations (other than those for units of measure) the first time they are used. Idiosyncratic abbreviations should not be used.

Drugs. Generic rather than trade names of drugs should be used. Trade or manufacturers' names are used only if the drug or equipment is experimental or unavailable in this country or if such information is crucial to the evaluation of the results or replication of the study.

References

References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. Do not arrange the list alphabetically.

References should be restricted to closely pertinent material. **Accuracy of citation is the author's responsibility.** References should conform exactly to the original spelling, accents, punctuation, etc. Authors should be sure that all references listed have been cited in text.

Personal communications, unpublished manuscripts, manuscripts submitted but not yet accepted, and similar unpublished items should not appear in the reference list. Such citations may be noted in text. It is the author's responsibility to obtain permission to refer to another individual's unpublished observations. Manuscripts that are actually "in press" may be cited as such in the reference list; the name of the journal or publisher and location must be included.

Type references in the style shown below, **double-spaced throughout**. List up to three authors; designate one or more authors past the third as "et al." Abbreviations of journal names should conform to the style used in *Index Medicus*; journals not indexed there should not be abbreviated.

1. Glick ID, Hargreaves WA, Drues J, et al: Short versus long hospitalization, a prospective controlled study, VII: two year follow-up results for nonschizophrenics. *Arch Gen Psychiatry* 1977; 34:314-320
2. McNamara JR (ed): *Behavioral Approaches to Medicine*. New York, Plenum Press, 1979
3. Janowsky DS, Judd LL, Huey L, et al: Effects of naloxone in normal, manic and schizophrenic patients: evidence for alleviation of manic symptoms, in *Endorphins in Mental Health Research*. Edited by Usdin E, Bunney WE Jr, Kline NS. New York, Oxford University Press, 1979

TABLES AND FIGURES

The *Journal* does not publish tables or figures that have appeared in other English-language publications. Tables and figures that duplicate 1) material contained in text or 2) each other will not be used. Authors will be asked to delete tables and figures that contain data which could be given succinctly in text. Each table and figure should be understandable without reference to the text; a descriptive, concise title should be included and units of measurement should be specified. Consult recent issues of the *Journal* for format. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. **A copy of each table and figure must be included with each copy of the manuscript.**

Tables

Tables should be double-spaced, no wider than 120 typewriter characters, including spaces, and no longer than 70 lines. Values expressed in the same unit of measurement should read down, not across; when percentages are given, the appropriate numbers must also be given.

Figures

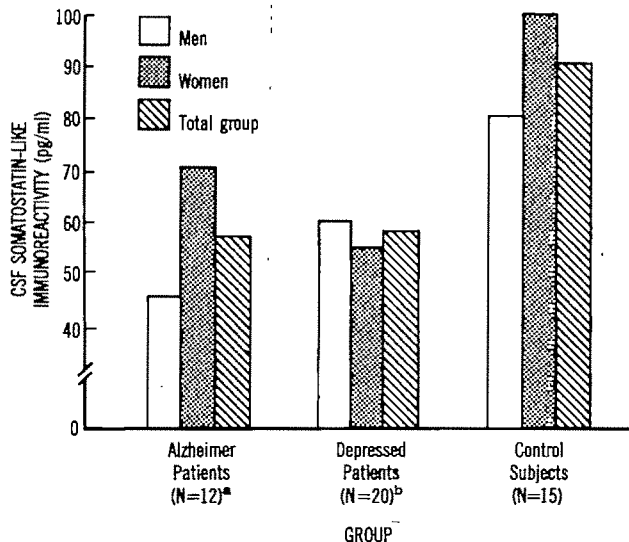
Figures are considered as text and are subject to revision by the authors upon recommendation of the Editors. Figures should, however, be professionally prepared. Glossy or other camera-ready prints should accompany the submitted manuscript. Computer-generated figures that do not meet quality printing standards will be returned for revision. The first author's name, the title of the paper, the figure number, and the top of the figure should be noted on a label affixed to the back of each figure. All figure titles and footnotes should be typed and sent together on a separate page.

The *Journal* does publish color illustrations. However, the cost to publish them, including reprint charges, will be the responsibility of the authors. An estimate of the cost will be provided to the authors at the time of first decision.

Format. Figures are visual expressions of data trends or relationships. Figures that represent numerical data which could be expressed more succinctly or clearly in tabular form should be converted to tables. Line graphs should show change in continuous variables; comparisons of like values in different groups should be presented as bar graphs. Graphs containing stacked bars are unacceptable; the different segments of each bar should be presented side by side.

Lettering. Figure type should be sans serif and should be large enough to remain legible after the figure is reduced; most figures taking up the width of a vertical manuscript page are reduced to a width of 19.5 picas (3/4 inches), and those requiring a horizontal manuscript page are usually re-

FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



^aSignificant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).

^bSignificant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

duced to 40.5 picas (6¾ inches). When space on the horizontal axis is insufficient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

Other. The following are additional specific requirements. Please refer to the example given above.

1. Do not use solid black shading; rather, include outlined white among shadings.

2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.

3. Error bars should not be used.

4. Do not extend the vertical or horizontal axis of a graph beyond the point needed for the data shown.

5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.

6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.

7. To save space, related figures that have the same vertical or horizontal axis should be combined. Headings identifying the segments of the combined figure should appear in the upper lefthand corners of the individual segments (in lower-case type with an initial upper-case letter).

8. The key should appear within or above the figure but should not be wider than the figure itself. Avoid placing other type (e.g., number of subjects, statistical values) within the axes of a graph.

9. Footnotes (including p values) should be cited with superscript letters in the title or body of the figure and should be listed in the order in which they are cited in the figure.

PROCESSING OF ACCEPTED MANUSCRIPTS

Manuscripts are accepted with the understanding that the Editor and the editorial staff have the right to make revisions aimed at greater conciseness, clarity, and conformity with *Journal* style. Accepted papers will be edited and sent to the first-named (or corresponding) author for corrections and answers to editorial queries. No proofs are sent to authors. Authors who will be away from their offices for a long period or who change address after notification of acceptance should inform the *Journal* staff.

PERMISSION TO REPRINT

Written permission to reprint material published in the *Journal* must be secured from the APA Periodicals Services Division, 1400 K Street, N.W., Washington, DC 20005; telephone: (202)682-6156. There is usually a charge for such permission, except for nonprofit classroom or library reserve use by instructors and educational institutions or for authors who wish to reprint their own material. Requests will be facilitated if accompanied by written permission from the author of the material.

REPRINTS

No reprints are furnished gratis. An order form for reprints will be sent to the corresponding author before publication of the paper. The printer usually mails reprints approximately 6 weeks after the article has been published. Reprints of items in the Book Forum and Letters to the Editor sections are not available.

PSYCHIATRISTS

BOSTON

Fulltime and parttime psychiatrists sought for exciting mix of public and private practice. Academic appointment at the Boston University Medical Center for qualified applicants, opportunity for research and private practice and inpatient/ambulatory care at public mental health facility. Opportunity to be part of a growing group practice with ownership of stock available. A non-profit low overhead research institute is affiliated with the practice to accept grants for physicians. Superb compensation package includes fringe benefits tailored to individual needs. Minority and Spanish-speaking physicians especially sought.

Send CV in confidence to:
Richard Pillard, M.D.
Boston Psychiatric Group, P.C.
Room 905 JP
85 E. Newton St.
Boston, MA 02118.

An Affirmative Action Employer.

STAFF PSYCHIATRIST

Comprehensive Mental Health Center is seeking staff psychiatrist to provide a wide range of services, including medical evaluation, psychotherapy, clinical supervision, and staff development.

Must be board certified or board eligible. Must have an Indiana license.

Competitive salary and fringe benefit program offered.

Send letter of application and vitae to:

LaNita M. James
Human Resources Department
Gary Community Mental Health Center, Inc.
1100 West 6th Avenue
Gary, Indiana 46402
(219) 885-4264

EOE/MF



GARY COMMUNITY
MENTAL HEALTH
CENTER INC.

PSYCHIATRIST

Swope Parkway Health Center has an immediate opening for a full-time/part-time psychiatrist. Must be board-certified or board-eligible. Must be licensed in Missouri.

Swope Parkway Health Center is JCAHO-accredited, ambulatory health center and a community mental health center providing a wide range of mental health services including:

- outpatient
- drug and alcohol
- partial hospital
- children's services
- residential care
- various preventive programs

In addition, the Health Center provides services in pediatrics, internal medicine, OB/GYN, podiatry, dental, and optometry services. Hospital privileges in two area hospitals. Center provides malpractice, CME, health/life insurance, pension, disability, holidays, and competitive salary.

Send curriculum vitae to:

Cheryl Kelow
Personnel Director
Swope Parkway Health Center
4900 Swope Parkway
Kansas City, MO 64130
(816) 923-4545, ext. 225

PSYCHIATRIST

The Center for Mental Health, Inc. a comprehensive mental health center accredited by JCAHO is seeking a psychiatrist to provide diagnostic assessment and treatment. Candidates will work under the supervision of the Medical Director and be required to share on-call rotation with other members of the medical staff. Additional responsibilities include medical and community liaison/consultation, court evaluations/assessments, and in-service training. Individuals should possess the ability to work well in a multi-disciplinary team setting.

An M.D is required with a residency in psychiatry (child residency or adolescent experience preferred). Candidates should hold an unlimited license to practice medicine in Indiana, be board eligible and preferably Board certified in psychiatry.

The Center is located in Anderson, IN, an urban, family oriented community located 30 miles NE of Indianapolis. We offer excellent salaries, fringe benefits and working conditions. If you would like to be considered for this opportunity, please submit a resume to:

P.O. Box 1258, Anderson, IN 46015
EOE

INDEX TO ADVERTISERS

MAY 1989

The publication of an advertisement in this journal does not imply endorsement of the product or service by the American Psychiatric Association.

AUSTEN RIGGS CENTER	A39
BIO-LOGIC	C3
BOLAR PHARMACEUTICALS	A47
CADWELL LABS	A17
CAMBRIDGE UNIV. PRESS	A37
THE CHILDREN'S CAMPUS	A51
CIBA-GEIGY PHARMACEUTICALS Treatment IND	A25
DISTA PRODUCTS/DIV. OF ELI LILLY & CO. Prozac	A40-A42
DORSEY DIVISION/SANDOZ PHARMACEUTICALS Mellaril	A34
Pamelor	A19-A20
ECS/ELECTRONIC CHART	A13
EINSTEIN MEDICAL/PHILADELPHIA PSYCHIATRIC CENTER	A37, A39
ELCOT	A33
EMPLOYMENT OPPORTUNITIES	A22, A29, A59-A60
HOSPITAL CORP. OF AMERICA	A29
INSTITUTE OF LIVING	A11
LEDERLE LABORATORIES Asendin	A53-A54
LEMMON COMPANY Orap	A27-A28
MCNEIL PHARMACEUTICAL Haldol Decanoate	A23-A24, A35-A36
MEAD JOHNSON PHARMACEUTICAL Buspar	A21-A22
Desyrel	C4
MECTA CORPORATION	A39
MEETING AND CONFERENCES	A12, A14, A32
PDLA	A2
PLENUM PUBLISHING	A13
ROCHE LABORATORIES Valium	A9-A11
ROERIG DIV./PFIZER, INC. Navane	A6-A8
Sinequan	A30-A32
ST. FRANCIS HOMES	A52
SMITH, KLINE, FRENCH LABS Stelazine	A45-A46
SOMATICS, INC.	A13
THE UPJOHN COMPANY Xanax	A43-A44
WYETH-AYERST LABORATORIES Ativan	C2-A1
Ativan Injection IM	A48-50

ASSISTANT PROFESSOR PSYCHIATRY

University of Minnesota's Department of Psychiatry seeks a Psychiatrist to fill a probationary, tenure-track position as assistant professor. The position entails commitment to research and training. The successful applicant will share with other faculty members responsibility for a treatment team involved in the care of psychiatry, especially substance abuse disorder, and cross-cultural psychiatric care. This team, in addition to treating patients, has the responsibility of training residents, medical students, and psychology interns.

Applicants should be board-eligible, have completed psychiatric residency, and demonstrate involvement in quality psychiatric research accepted or published in peer-reviewed journals.

Send resume to:

Joseph Westermeyer, M.D.
UMHC Box 393
University of Minnesota Hospitals
Minneapolis, MN 55455

The University of Minnesota is an equal opportunity educator and employer and specifically invites and encourages applications from women and minorities.



ECONOMICS OF SCIENTIFIC JOURNALS

"This publication is an in-depth source for anyone who wants to learn about the inner workings of scientific journal publishing. Although it deals mostly with society, not-for-profit publishing, it provides the reader with the general philosophy and methods used by most commercial publishers as well."

--Society for Scholarly Publishing Letter

CONTENTS: Member Subscriptions • Single Issues and Back Volumes • Reprints • Advertising in Scholarly Journals • Page Charges • Journal Income: a Multipublisher's View • Editorial Operations • Copy Editing • Purchasing Typesetting Separately from Printing • Presswork, Binding, and Paper • Distribution and Postage • Subscription Fulfillment • Budgeting, Accounting, and Financial Planning • Marketing the Scientific Journal • Subject Index

Paperbound; ISBN: 0-914340-03-4; Publication date: December 1982; Trim size: 6 x 9 inches; 106 pages

Regular Price: \$11.95 (10% discount on 10 or more copies delivered to one address)

CBE Member Discount Price: \$10.75 (single copy paid by personal check)

Terms of Sale: All sales final; no returns.

Prepayment required; U.S. currency drawn on a U.S. bank. Price includes BOOK RATE postage.

For faster delivery--first class, air mail, or UPS available at additional charge (book weight 8.5 oz).

Maryland residents, please add 5% sales tax.

COUNCIL OF BIOLOGY EDITORS, INC.
9650 Rockville Pike, Bethesda, MD 20814

THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 146, Number 6 June 1989

In this issue:

Sleep Disturbance as the Hallmark of Posttraumatic Stress Disorder

By Richard J. Ross, William A. Ball, Kenneth A. Sullivan, et al.

Psychiatry in Africa: An Overview

By A.O. Odejide, L.K. Oyewunmi, and J.U. Ohaeri

Official Journal of the American Psychiatric Association

Her anxiolytic
is working—
but she's alert,
functioning, and
at no risk of a
benzodiazepine
withdrawal
syndrome when
therapy ends.



That's
Efficacy!

BuSpar® (buspirone HCl)

References: 1. Rickels K, et al. Buspirone and diazepam in anxiety: A controlled study. *J Clin Psychiatry* 1982; 43(12, Sec 2): 81-86. 2. Newton RE, et al. A review of the side effect profile of buspirone. *Am J Med* 1986; 80(suppl 3B): 17-21. 3. Lucki I, et al. Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987; 23: 207-211. 4. Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987; 82(suppl 5A): 20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: General—Interference with cognitive and motor performance: Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the

syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B. Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age. **Use in the Elderly—**No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): Commonly Observed—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation in-

Effective choice for anxiety

BuSpar[®]

Tablets
5 mg and 10 mg

(buspirone HCl)

for a different kind of calm



BuSpar cuts the link between efficacy and CNS-depressant effects

BuSpar relieves anxiety¹ and returns your patient to normal activity

... with no more drowsiness (10%) than induced by placebo (9%)²

... without significant cognitive³ or functional impairment*

... without a benzodiazepine withdrawal syndrome on discontinuation⁴

Well tolerated

The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness (12%), nausea (8%), headache (6%), nervousness (5%), lightheadedness (3%), and excitement (2%).

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

cluded: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular*: Tachycardia/palpitations 1%. *CNS*: Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT*: Blurred vision 2%. *Gastrointestinal*: Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal*: Musculoskeletal aches/pains 1%. *Neurological*: Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin*: Skin rash 1%. *Miscellaneous*: Headache 6%, fatigue 4%, weakness 2%, sweating/flushing 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain, infrequent: syncope, hypotension, hypertension, rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances, infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures, rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of

breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: Controlled Substance Class—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: Signs and Symptoms—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

Mead Johnson
PHARMACEUTICALS
A Bristol-Myers Company
Evansville, Indiana 47721

Easy
to
break

Easy
to
take

NEW 300 mg

Desyrel[®] DIVIDOSE[®]

(trazodone HCl) 150 mg and 300 mg tablets



- ▶ More convenient for patients needing over 150 mg Desyrel a day.
- ▶ Easy to titrate — each tablet provides four dosage strengths: three 100 mg doses, two 150 mg doses, one 200 mg plus one 100 mg dose, or one 300 mg dose.
- ▶ More economical than other forms of Desyrel and Desyrel Dividose.

Mead Johnson
PHARMACEUTICALS



A Bristol-Myers Company
Evansville, Indiana 47721



THE AMERICAN JOURNAL OF PSYCHIATRY

EDITOR

John C. Nemiah, M.D.

DEPUTY EDITOR

Morris A. Lipton, Ph.D., M.D.

BOOK FORUM EDITOR

Nancy C. Andreasen, M.D., Ph.D.

EDITORIAL STAFF

Managing Editor

Melanie M. Shipley

Assistant Managing Editor

Linda A. Loy

Senior Assistant Editors

Marianne K. Guerra

Laura M. Little

Jane Weaver

Assistant Editor

Marjorie M. Henry

Production Editor

Beverly M. Sullivan

Administrative Assistant

Cynthia A. Dispenza

Editorial Secretaries

Crystal Coleman

Jennifer DuPree

ASSOCIATE EDITORS

Hagop S. Akiskal, M.D.

Ross J. Baldessarini, M.D.

Elissa P. Benedek, M.D.

Jonathan F. Borus, M.D.

Kenneth L. Davis, M.D.

Lewis L. Judd, M.D.

Toksoz Byram Karasu, M.D.

Herbert Y. Meltzer, M.D.

Judith L. Rapoport, M.D.

Loren H. Roth, M.D., M.P.H.

Lorraine D. Siggins, M.D.

Charles E. Wells, M.D.

Richard Jed Wyatt, M.D.

STATISTICAL EDITORS

John J. Bartko, Ph.D.

Lee Gurel, Ph.D.

FORMER EDITORS

Amariah Brigham, M.D.

1844-1849

T. Romeyn Beck, M.D.

1849-1854

John P. Gray, M.D.

1854-1886

G. Alder Blumer, M.D.

1886-1894

Richard Dewey, M.D.

1894-1897

Henry M. Hurd, M.D.

1897-1904

Edward N. Brush, M.D.

1904-1931

Clarence B. Farrar, M.D.

1931-1965

Francis J. Braceland, M.D.

1965-1978

The American Journal of Psychiatry, ISSN 0002-953X, is published monthly by the American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005. Subscriptions: U.S. \$56.00 (student \$28.00) per year, Canada and foreign \$71.00 (student \$43.00); single issues: U.S. \$7.00, Canada and foreign \$8.00.

Business communications, changes of address, and questions about subscriptions from APA members should be directed to the Division of Member Services: (202) 682-6090. Communications from nonmember subscribers should be directed to the Circulation Department: (202) 682-6158. Authors who wish to contact the *Journal* editorial office should call (202) 682-6020.

Business Management: Nancy Frey, Director, Periodicals Services; Laura G. Abedi, Advertising Production Manager: (202) 682-6154; Beth Prester, Director, Circulation; Karen Loper, Promotion Manager; Jackie Coleman, Fulfillment Manager.

Advertising Sales: Raymond J. Purkis, Director, 2444 Morris Avenue, Union, NJ 07083; (201) 964-3100. Steve Jones, APA, 1400 K St., N.W., Washington, DC 20005; (202) 682-6329.

Type set by Byrd Data Imaging Group, Richmond, VA. Printed by The William Byrd Press, Inc., Richmond, VA.

Second-class postage paid at Washington, DC, and additional mailing offices. POSTMASTER: Send address changes to *The American Journal of Psychiatry*, Circulation Department, American Psychiatric Association, 1400 K St., N.W., Washington, DC 20005.

Indexed in *Abstracts for Social Workers*, *Biological Abstracts*, *Chemical Abstracts*, *Chicago Psychoanalytic Literature Index*, *Cumulative Index to Nursing Literature*, *Excerpta Medica*, *Hospital Literature Index*, *Index Medicus*, *International Nursing Index*, *Nutrition Abstracts*, *Psychological Abstracts*, *Science Citation Index*, and *Social Sciences Index*.

The American Psychiatric Association does not hold itself responsible for statements made in its publications by contributors or advertisers. Unless so stated, material in the *Journal* does not reflect the endorsement, official attitude, or position of the American Psychiatric Association or of the *Journal*'s Editorial Board.

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by APA for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of \$00.75 per copy is paid directly to CCC, 21 Congress St., Salem, MA 01970. 0002-953X/89/\$00.75.

This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. APA does not require that permission be obtained for the photocopying of isolated articles for nonprofit classroom or library reserve use; all fees associated with such permission are waived.

Copyright © 1989 American Psychiatric Association.

THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 146, Number 6 June 1989

- | | | |
|----------------------|-----|---|
| EDITORIAL | 695 | Sleep Disturbance in Posttraumatic Stress Disorder: Pathogenetic or Epiphenomenal? <i>Charles F. Reynolds III</i> |
| SPECIAL ARTICLES | 697 | Sleep Disturbance as the Hallmark of Posttraumatic Stress Disorder
<i>Richard J. Ross, William A. Ball, Kenneth A. Sullivan, and Stanley N. Caroff</i> |
| | 708 | Psychiatry in Africa: An Overview <i>Adebayo Olabisi Odejide, Lamidi Kolawole Oyewunmi, and Jude Uzoma Ohaeri</i> |
| REGULAR ARTICLES | 717 | A Prospective Analysis of 24 Episodes of Neuroleptic Malignant Syndrome <i>Patricia Rosebush and Thomas Stewart</i> |
| | 726 | Changing Patterns of Neuroleptic Dosage Over a Decade
<i>Gerard T. Reardon, Arthur Rifkin, Arthur Schwartz, Arthur Myerson, and Samuel G. Siris</i> |
| | 730 | Serotonergic Measures in the Brains of Suicide Victims: 5-HT ₂ Binding Sites in the Frontal Cortex of Suicide Victims and Control Subjects
<i>Ramesh C. Arora and Herbert Y. Meltzer</i> |
| | 737 | HIV-Related Symptoms and Psychological Functioning in a Cohort of Homosexual Men <i>David G. Ostrow, Andrew Monjan, Jill Joseph, Mark VanRaden, Robin Fox, Lawrence Kingsley, Janice Dudley, and John Phair</i> |
| | 743 | TSH Response to TRH in Depression With and Without Panic Attacks
<i>Gregory M. Gillette, James C. Garbutt, and Dana E. Quade</i> |
| | 749 | Hypnotic Alteration of Somatosensory Perception <i>David Spiegel, Pierre Bierre, and John Rootenberg</i> |
| | 755 | Physical and Sexual Assault Histories Among Psychiatric Outpatients
<i>Andrea Jacobson</i> |
| COMMENTARY | 759 | Child Psychiatry Fellowship Training: A Crisis in Recruitment and Manpower <i>Eugene V. Beresin and Jonathan F. Borus</i> |
| BRIEF COMMUNICATIONS | 764 | Clinical Predictors of Recurrence in Depression <i>Donna E. Giles, Robin B. Jarrett, Melanie M. Biggs, David S. Guzick, and A. John Rush</i> |
| | 768 | Treatment of Body-Dysmorphic Disorder With Serotonin Reuptake Blockers <i>Eric Hollander, Michael R. Liebowitz, Ronald Winchel, Almuth Klumker, and Donald F. Klein</i> |
| | 771 | Experiences of a Paraplegic Psychiatry Resident on an Inpatient Psychiatric Unit <i>Beryl B. Lawn</i> |

CLINICAL AND
RESEARCH REPORTS

- 775 Patterns of Psychotherapy Utilization *Kenneth I. Howard, Christine V. Davidson, Michael T. O'Mahoney, David E. Orlinsky, and Kevin P. Brown*
- 779 Hypersensitivity to Carbon Dioxide in Panic Disorder *Laszlo A. Papp, Raymond Goetz, Randolph Cole, Donald F. Klein, Fanchea Jordan, Michael R. Liebowitz, Abby J. Fyer, Eric Hollander, and Jack M. Gorman*
- 782 ECT for Major Depression in Four Patients Infected With Human Immunodeficiency Virus *Frederick W. Schaerf, Robyn R. Miller, John R. Lipsey, and Robert W. McPherson*
- 785 Age at Onset in Late-Life Delusional Depression *J. Craig Nelson, Yeates Conwell, Kathy Kim, and Carolyn Mazure*
- 787 CSF GABA in Caregiver Spouses of Alzheimer Patients *Nunzio Pomara, Dennis Deptula, Matthew P. Galloway, Peter A. LeWitt, and Michael Stanley*
- 789 Self-Cutting After Rape *Gail S. Greenspan and Steven E. Samuel*

BOOK FORUM

791

LETTERS
TO THE EDITOR

801

- 818 Corrections: Peter Ostwald: review of *Turn-of-the-Century Cabaret: Paris, Barcelona, Berlin, Munich, Vienna, Cracow, Moscow, St. Petersburg, Zurich*, by Harold B. Segel (1988; 145:1602-1603); George R. Brown and James R. Rundell: "Suicidal Tendencies in Women With Human Immunodeficiency Virus Infection" (letter) (1989; 146:556-557)

OTHER

- A11 Officers of the American Psychiatric Association
- A18 Calendar
- A30 Books Received
- A38 *British Journal of Psychiatry* Contents (April 1989)
- A50 Index to Advertisers

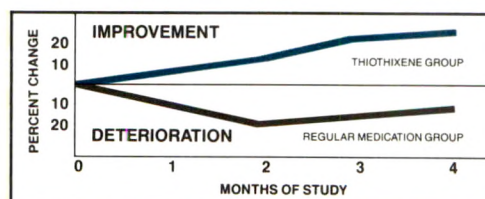


"IT FEELS GOOD TO FEEL USEFUL AGAIN"

For the chronic schizophrenic patient, Navane can mean more competent work performance,^{1,2} and a smoother path towards social recovery. Navane may help improve the ability to concentrate, and promote a better attitude toward work and co-workers.¹⁻³

Anticholinergic⁴ and cardiovascular^{5,6} side effects in patients treated with Navane are reported infrequently. Should extrapyramidal symptoms occur, they usually can be controlled.

**27% rise in work output
compared to baseline shown
in patients switched to Navane^{2,3}**



(Adapted from DiMascio and Demigian^{2,3})

Forty-two psychotic male and female patients under age 55 were entered in this study on a nonblind basis, and randomly assigned to their regular medication or switched to thiothixene. Patients were evaluated at baseline and on a daily basis, and periodically rated on the Global Improvement and Brief Psychiatric Rating Scales.

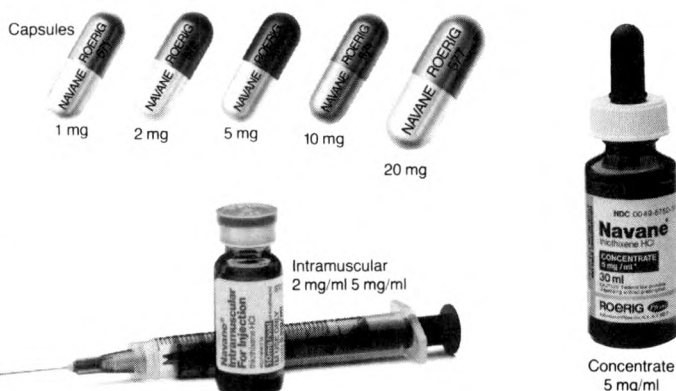
In schizophrenia,
Navane[®] (thiothixene)(thiothixene HCl)

Please see brief summary of NAVANE[®] (thiothixene/thiothixene HCl) prescribing information on adjacent page.

Navane®

(thiothixene) (thiothixene HCl)

It feels good to feel useful again



References: 1. Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2. DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3. DiMascio A, Demirjian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association, Washington, DC, May 3-6, 1971. 4. Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients. In Lehmann HE, Ban TA (eds): *The Thioxanthenes. Modern Problems of Pharmacopsychiatry*. Basel, Switzerland, S. Karger, 1969, vol 2, pp 45-52. 5. Dillenkoffer RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of the American Psychiatric Association, Dallas, May 1-4, 1972. 6. Data available on request from Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.

Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged

periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: Note: Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Non-specific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmic involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecostasia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

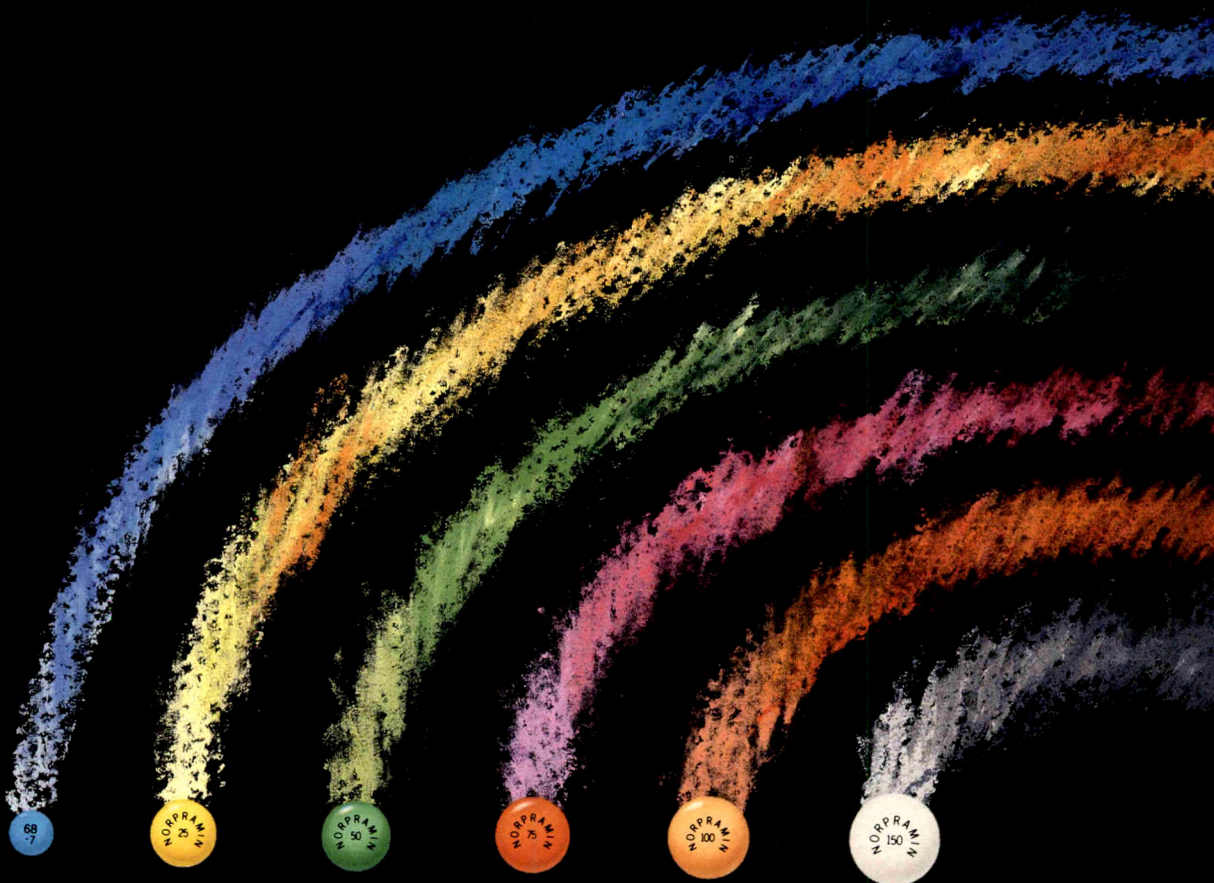
NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

ROERIG Pfizer

A division of Pfizer Pharmaceuticals
 New York, New York 10017



**A spectrum of reasons
to write D.A.W.
when you prescribe**



Norpramin[®]

10, 25, 50, 75, 100, 150 mg

(desipramine hydrochloride tablets USP)

A logical choice among antidepressants

A 25-year history of proven clinical usefulness with unsurpassed **flexibility of dosage** provided by 6 tablet strengths, **color coded** to ensure exact identification. It also offers **dose equivalence** that permits prescribing one tablet of greater strength in place of multiple doses of lesser strengths, resulting in **increased patient compliance** and greater than **20% cost savings**.

Merrell Dow U.S.A.

(Brief Summary of Prescribing Information appears on the next page.)



Ensure the maximum benefits of Norpramin by specifying "Dispense As Written."

- A 25-year record of efficacy in relieving the symptoms of depression*
- Less anticholinergic activity than amitriptyline or doxepin*
- Usually no excessive daytime drowsiness (see Warnings)†

Norpramin (desipramine hydrochloride tablets USP)

*References supporting these statements available from MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242.

†Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

Merrell Dow U.S.A.
Division of Merrell Dow Pharmaceuticals Inc.

Norpramin®

10, 25, 50, 75, 100, 150 mg
(desipramine hydrochloride tablets USP)

Norpramin® (desipramine hydrochloride tablets USP)

BRIEF SUMMARY

CAUTION: Federal law prohibits dispensing without prescription.

INACTIVE INGREDIENTS

The following inactive ingredients are contained in all dosage strengths: acacia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Metabolism

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Additional information on metabolism appears in Full Prescribing Information.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hypertensive crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

1. Extreme caution should be used when this drug is given in the following situations:
 - a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
 - b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
 - c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
 - d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. **USE IN PREGNANCY**
Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**
Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdose.

PRECAUTIONS

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. There has been a report of an "acute collapse" and

"sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity. (See WARNINGS, Use in Children.)

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure, constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecostasia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSEAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evaluation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here. Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

- (a) **Dialysis:** Desipramine is found in low concentration in the serum, even after a massive oral dose. In vitro experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.
- (b) **Pharmacologic treatment of shock:** Since desipramine potentiates the action of such vasopressor agents as levaterenol and metaraminol, they should be used only with caution.
- (c) **Pharmacologic control of seizures:** Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.
- (d) **Pharmacologic control of cardiac function:** Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

Product Information as of January, 1989

Y398D

MERRELL DOW U.S.A.
A Division of Merrell Dow Pharmaceuticals Inc.
Cincinnati, Ohio 45215

Merrell Dow U.S.A.

The American Psychiatric Association

1400 K Street, N.W., Washington, D.C. 20005

OFFICERS 1988-1989

President: Paul J. Fink
President-Elect: Herbert Pardes
Vice-President: Allan Beigel
Vice-President: Lawrence Hartmann
Secretary: Elissa P. Benedek
Treasurer: Alan Levenson

ASSEMBLY

Speaker: John S. McIntyre
Speaker-Elect: Gerald Flamm
Recorder: Edward Hanin

BOARD OF TRUSTEES

Robert J. Campbell III
 Frederick Gottlieb
 Shelly F. Greenfield
 Merlin Johnson
 Linda Logsdon
 Rodrigo A. Munoz
 Carol C. Nadelson
 Pete C. Palasota
 Robert O. Pasnau
 George H. Pollock
 Herbert S. Sacks
 Douglas A. Sargent
 Chester W. Schmidt, Jr.
 William L. Webb, Jr.

MEDICAL DIRECTOR'S OFFICE

Medical Director: Melvin Sabshin
Deputy Medical Directors: John M. Hamilton
 Harold A. Pincus
 Carolyn B. Robinowitz
 Jeanne Spurlock

CHAIRPERSONS OF COUNCILS, COMMISSIONS, COMMITTEES, AND TASK FORCES

CONSTITUTIONAL COMMITTEES

Budget	Steven S. Sharfstein
Constitution and By-Laws	Ralph A. O'Connell
Elections	Bernice B. Elkin
Ethics	Robert J. McDewitt
Tellers	Edward C. Kirby, Jr.
Membership	Michael J. Vergare
Nominating	George H. Pollock
Reference	Herbert Pardes
Resource Development	Howard F. Wallach

COUNCIL ON AGING

Nursing Homes and Elderly Mentally Ill	Gene David Cohen
Education and Training in Geriatric Psychiatry	Benjamin Liptzin
Geriatric Psychiatry in the Public Mental Health Sector	Charles A. Shamoian
Ethnic Minority Elderly	Barry Steven Fogel
White House Conference on Aging	Kenneth Mark Sakauye
Reimbursement for Elderly Mentally Ill	Sanford Irwin Finkel
	Howard Hirsch Goldman

COUNCIL ON CHILDREN, ADOLESCENTS, AND THEIR FAMILIES

Chronically Ill and Emotionally Handicapped Children	Larry B. Silver
Confrontational Therapies	Cynthia R. Pfeffer
Juvenile Justice Issues	Mark J. Blorcky
Psychiatry and Mental Health in Schools	William M. Buzogany
Family Violence and Sexual Abuse	Irving H. Berkovitz
Psychiatric Aspects of New Reproductive Technologies	Sandra J. Kaplan
	Miriam B. Rosenthal

COUNCIL ON ECONOMIC AFFAIRS

Financing and Marketing	Donald J. Scherl
JCAH Standards for Hospital-Based, Hospital-Related Services	Robert O. Friedel
Interprofessional Affairs	Boris M. Astrachan
Social Security Income/Disability Insurance	Mildred Mitchell-Bateman
Prospective Payment Issues	Arthur T. Meyerson
Future Trends in Private Insurance	Joseph T. English
Psychiatrist Payment	Robert W. Gibson
Quality Assurance	Boris M. Astrachan
	George Wilson

COUNCIL ON INTERNAL ORGANIZATION

Arrangements	Ronald A. Shellow
Scientific Program	Kathleen Bell Unger
Film	Mel Blaustein
Scientific and Educational Exhibits	Allan Tasman
Video	Bernard Martin Morenz
Information Systems	Jean Patricia Goodwin
	Donald Carl Fidler
	Wanda W. Winn

Foundations' Fund Prize for Research in Psychiatry

Grants and Awards	Ira D. Glick
Manfred S. Guttmacher Award	Alan I. Levenson
Marie H. Eldredge Award	William H. Reid
Hospital and Community Psychiatry	Bernice E. Coleman
Achievement Awards	
Isaac Ray Award	Doris Lee Dickens
Ittleson Award	Richard T. Rada
Weinberg Memorial Award	Dennis P. Cantwell
McGavin Award	Sanford I. Finkel
Vestermark Award	Mina Karen Dulcan
Samuel G. Hibbs Award	Bryce Templeton
Advertising	Steven M. Mirin
Headquarters	Will D. Strathmann
Member Life, Accident, and Health Insurance	Raymond I. Band
Special Benefit Programs	Harvey Bluestone
Personnel	Abram M. Hostetter
Advertisers and Exhibitors	Maurice J. Martin
Telemedical Services	Henry H. Work
History and Library	Jane H. Preston
Exhibits Advisory	Lucy D. Ozarin
Friends of the APA	Joseph H.B. Honnigford
PIA Foundation Hospital Research Awards	Evelyn P. Ivey-Davis
	H. Richard Lamb

COUNCIL ON INTERNATIONAL AFFAIRS

Abuse and Misuse of Psychiatry and Psychiatrists	Harold M. Visorsky
Inter-American Council Liaison	Michael R. Zales
Human Rights	Jorge A. Costa e Silva
Psychosocial Aspects of the Middle East Process	Lawrence Hartmann
International Education	George Tarjan
Joint Meeting in Germany in 1990	Normund Wong
	Eric Plaut

COUNCIL ON MEDICAL EDUCATION AND CAREER DEVELOPMENT

Administrative Psychiatry	Joel Yager
Medical Student Education	Stephen L. Rachlin
Graduate Education	Leah Joan Dickstein
Continuing Education	Stefan P. Stein
Consultation-Liaison Psychiatry and Primary Care Education	John W. Goethe
Impaired Physician	Troy L. Thompson II
Communication-Between APA and ABPN	Robert W. McDermott
Recertification	Richard I. Shader
Independent Study	Joe P. Tupin
PKSAP-VI	Keith Hadley Johansen
Residents	Gordon Darrow Strauss
Post Residency Fellowship Programs	Henry Carl Emmons
	George H. Pollock

APA/Burroughs Wellcome Fellowship	Roger Peele	Practice of Psychotherapy	Marcia Kraft Goin
APA/Mead Johnson Fellowship	James T. Barter	Practice Issues in Organized/Managed Care	Haroutun Babigian
APA/NIMH Minority Fellowship Program	Charles A. Pinderhughes	COUNCIL ON PSYCHIATRY AND LAW	Howard V. Zonana
Psychiatric Leadership in Public Mental Health Programs	Robert L. Leon	Confidentiality	Aron S. Wolf
Education Activities for DSM-III-R	Michael A. Fauman	Treatment Records in Child Custody Disputes	Carl P. Malmquist
COUNCIL ON NATIONAL AFFAIRS	Lindbergh S. Sata	Psychiatric Diagnoses in the Courts	Seymour L. Halleck
Abuse and Misuse of Psychiatry in U.S.	Roger Dale Walker	COUNCIL ON RESEARCH	John E. Adams
Asian-American Psychiatrists	Joyce S. Kobayashi	Electroconvulsive Therapy	Richard D. Weiner
Black Psychiatrists	Ernest A. Kendrick	Long-Term Effects of Lithium on Kidney	George R. Heninger
American Indian and Alaskan		Treatments of Psychiatric Disorders	T. Byram Karasu
Native Psychiatrists	Linda K. Cross	Tardive Dyskinesia	John Michael Kane
Foreign Medical Graduates	Walter Weintraub	Psychosocial Treatment Research	John P. Docherty
Religion and Psychiatry	Marc Galanter	Prevention Research	Robert M. Rose
Hispanic Psychiatrists	Eduardo R. Val	Biographical Directory	Robert Alan Dorwart
Women	Nada Logan Storland	Benzodiazepine Dependency	Carl Salzman
Gay, Lesbian, and Bisexual Issues	James Paul Krajewski	Psychiatric Diagnosis and Assessment	Layton McCurdy
Occupational Psychiatry	Duane Q. Hagen	Research on Psychiatric Treatments	John M. Kane
Psychological Aspects of Nuclear Arms Development	Judith E. Lipton	DSM-IV	Allen J. Frances
Victimization	Martin Symonds	COMMISSION ON JUDICIAL ACTION	Paul Appelbaum
COUNCIL ON PSYCHIATRIC SERVICES	J. Frank James	CONSULTATION SERVICE BOARD	Dave M. Davis
Alcoholism	Richard J. Frances	ETHICS APPEALS BOARD	Elissa P. Benedek
Clinician Safety	William R. Dubin	JOINT COMMISSION ON PUBLIC AFFAIRS	Harvey L. Ruben
Drug Abuse	Edward Kaufman	JOINT COMMISSION ON GOVERNMENT RELATIONS	John J. McGrath
Rehabilitation	Arthur T. Meyerson	SPECIAL COMPONENTS	
State Mental Health Systems	Ernest W. Klatte	Board Committee on Insurance	Alan I. Levenson
American Hospital Association	Mark A. Gould	Investment Advisory Committee	Frederick Amling
Functions of the Hospital and Community	H. Richard Lamb	Long-Range Planning Committee	Robert O. Pasnau
Psychiatry Service, Journal, and Institute	Leonard I. Stein	Executive Compensation Committee	William L. Webb, Jr.
Institute on Hospital and Community Psychiatry Program	Ludwik S. Szymanski	Work Group on Federal Government	
Psychiatric Services for Mentally Retarded/	David L. Cutler	Organizational Structure	Daniel X. Freedman
Developmentally Disabled Adults	Frederick G. Guggenheim	Work Group on Codes and	
Chronically Mentally Ill	Boris G. Rifkin	Reimbursement	Chester W. Schmidt, Jr.
Veterans Administration Affairs	Henry C. Weinstein	Commission on AIDS	Stuart E. Nichols, Jr.
Private Practice	Leonora K. Petty		
Jails and Prisons			
Psychiatric Services in the Military			

Coming in the July 1989 issue of

THE AMERICAN JOURNAL OF PSYCHIATRY

Statutory Approaches to Limiting Psychiatrists' Liability for Their Patients' Violent Acts

By Paul S. Appelbaum, Howard Zonana, Richard Bonnie, et al.

Seasonality and Affective Illness

By Thomas A. Wehr and Norman E. Rosenthal

Alternatives to Lithium for Preventive Treatment of Bipolar Disorder

By Robert F. Prien and Alan J. Gelenberg

NOW AVAILABLE!
THE 5 mL MULTI-DOSE VIAL

- ☐ same 50 mg/mL concentration
- ☐ cost-effective
- ☐ increased convenience

For the schizophrenic patient

**Sustained drug levels
with a single monthly dose**

HALDOL[®] DECANOATE
(HALOPERIDOL) INJECTION

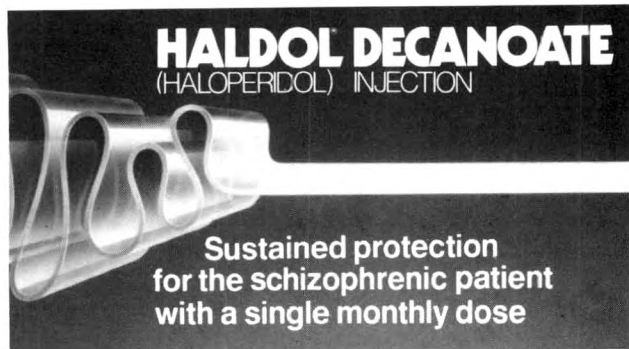
**Sustained protection
from relapse**

Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL[®] (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

 **McNEIL
PHARMACEUTICAL**
McNEILAB, INC., Spring House, PA 19477

© McNEILAB, INC., 1989



The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause

allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. **Withdrawal Emergent Neurological Signs—**Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. **Tardive Dyskinesia—**As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. **Tardive Dystonia—**Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. **Other CNS Effects—**Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.)

Cardiovascular Effects: Tachycardia, hypotension, hypertension and ECG changes. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice.

Dermatologic Reactions: Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Special Senses:** Cataracts, retinopathy and visual disturbances. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

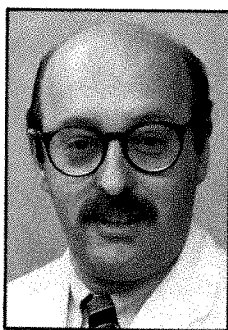
For information on symptoms and treatment of overdose, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

720/88

McNEIL
PHARMACEUTICAL
McNEILAB INC. Spring House PA 15747

Two Special Reasons It Will Be A Good Year For Psychiatry.



On May 8th, the American Psychiatric Association will present the third annual Psychiatric Institutes of America Foundation Awards for Hospital Psychiatry Research to Drs. Thomas N. Wise and Alexis Giese.

Dr. Wise is Chairman of the Department of Psychiatry at The Fairfax Hospital and Professor of Psychiatry at Georgetown University Hospital. Dr. Giese is medical director of the Psychiatric Day Treatment

Center at Georgetown University Hospital and an Instructor in the Department of Psychiatry at Georgetown University.



We look forward to the outcomes of their endeavors to optimize the care of patients in psychiatric hospitals. Psychiatric Institutes of America congratulates both of these professionals on their distinguished careers and outstanding achievements.



THE
INSTITUTE
OF
LIVING

**Topographical Mapping of Brain Electrical Activity:
Neuropsychiatric and Neuropsychological Applications**

A Symposium

Friday, October 13, 1989

8:30 a.m. - 5:00 p.m.

Hartford, Connecticut

Clinical Applications of Brain Electrical Activity Mapping in Psychiatry

Frank Duffy, M.D., BEAM Laboratory, Children's Hospital, Harvard Medical School

Event-Related Potential Abnormalities and Schizophrenia

Stephen Faux, Ph.D., Martha Shenton, Ph.D. and Robert McCarley, M.D.

Department of Psychiatry, Brocton V.A. Medical Center, Harvard Medical School

BEAM and Depressive Disorders: Clinical and Research Applications

*Russell Vasile, M.D. Department of Psychiatry, New England Deaconess Hospital,
Harvard Medical School*

Comparison of Topographical Distribution Findings in Schizophrenia and Depression

*Martin Ford, Ph.D., & John Goethe, M.D., Psychophysiology Laboratory, The Institute of
Living*

Mapping Behavior Into Brain: "Behavior Imaging"

Ruben Gur, Ph.D., Brain Behavior Laboratory, University of Pennsylvania

**Electrical Activity Mapping and Neuropsychological Dysfunction
in Deviant Sexual Behavior**

Leslie Lothstein, Ph.D., Martin Ford, Ph.D. and Geraldine Cassens, Ph.D.

Departments of Psychology and Psychophysiology, The Institute of Living

To preregister, send a check for \$135 payable to "The Institute of Living" Attn: Ms. Julie McDowell, Office of Public Relations, The Institute of Living, 400 Washington Street, Hartford, CT 06106. Fee increases to \$160 after July 15. Luncheon and refreshments provided. Seating limited to 200. For additional information, call (203) 241-6909.

PREREGISTRATION: Topographical Mapping of Brain Electrical Activity in Psychiatry

Name & Title _____

Address _____ City _____ State _____

Business Telephone _____ Zip _____

Organization _____



Thank You, Doctor...

Thank you, doctor, for helping us give Tommy the care he needed. Your referral to the St. Francis Homes was just the right prescription for our troubled son. His stay at St. Francis combined with your aftercare was exactly the right medicine.

Thanks to you and St. Francis, Tommy is a changed young man. After just a year in their therapy program and under their full-time supervision, Tommy is no longer the hostile and rebellious teenager we saw hanging around with the wrong crowd and getting deeper and deeper into trouble.

Thanks to you, we found a way to help a boy who didn't want to be helped. We're now a family once again.

**THE
ST. FRANCIS
HOMES**
EPISCOPAL



For information and referral, contact:

Richard W. Burnett, ACSW

Box 1340

Salina, Kansas 67402-1340

Call Toll Free — 1-800-423-1342

In New York — 1-800-822-4363

In Kansas — 913-825-0541

Ellsworth, KS • Salina, KS • Lake Placid, NY • JCAHO Accredited • CHAMPUS Certified

© 1988 St. Francis Homes 159

Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.

AUGUST

August 3–6, 4th International Congress on Pre and Perinatal Psychology, Amherst, Massachusetts. Contact University Conference Services, PPPANA CS 90-2N, 918 Campus Center, University of Massachusetts, Amherst, MA 01003; 413-545-2591.

August 7–12, international congress on "Therapy With Amino Acids and Analogues," Vienna. Contact Prof. G. Lubec, MA 17, Allgemeines Krankenhaus, Wahringer Gurtel 18-20, 1090 Wien, Austria.

August 21–25, World Congress on Mental Health, World Federation for Mental Health, Auckland, New Zealand. Contact Richard Hunger, World Federation for Mental Health, 1021 Prince Street, Alexandria, VA 22314-2971; or Dr. M. Abbott, Mental Health Foundation, P.O. Box 37-438 Parnell, Auckland, New Zealand.

August 26–30, annual meeting of Alcohol and Drug Problems Association of North America, Washington, D.C. Contact Jeffrey T. Kramer, Assistant Executive Director, 444 N. Capitol Street, NW, Suite 181, Washington, DC 20001; 202-737-4340.

August 27–September 2, 10th International Congress, International Association of Group Psychotherapy: "Encounter or Alienation," Amsterdam. Contact Jay W. Fidler, M.D., 362 Old York Road, Flemington, NJ 08822.

August 29–September 1, 1st Congress, World Union of Professions, Montreal. Contact Services de Congres GEMS, C.P. 1016, Succ. Snowdon, Montreal, P.Q., Canada H3X 3Y1; 514-485-0855.

SEPTEMBER

September 4–7, International Medical Congress on the Detection and Examination of Human Rights Violations, Copenhagen. Contact Jette Christiansen, Medical Congress on Human Rights, c/o Amnesty International, Medical Group, Frederiksborggade 1, 1360 Copenhagen K, Denmark; 01-11-89-29.

September 5–8, 4th Congress of the International Psychogeriatric Association, Tokyo. Contact Akira Homma, M.D., Department of Psychiatry, St. Marianna University School of

Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 213, Japan; 044-977-8111, Ext. 3200.

September 12–15, 3rd International Congress on Ethics in Medicine, Stockholm. Contact Third International Congress on Ethics in Medicine, Beth Israel Medical Center, 1st Avenue at 16th Street, New York, NY 10003; 212-420-4082.

September 14–16, 5th International Conference of Alzheimer's Disease International, Dublin. Contact Alzheimer's Disease International, Conference Secretariat, 12 Pembroke Park, Dublin 4, Ireland.

September 20–24, 1st European Congress of Ericksonian Hypnosis and Psychotherapy, Heidelberg, West Germany. Contact Burkhard Peter, Dipl.Psych., Milton Erickson Gesellschaft für klinische Hypnose (M.E.G.), Konradstr. 16, D-8000 München 40, West Germany; 089-2180-5175.

September 22–23, National Conference on Drug Abuse and Sport: Prevention, Intervention, Elimination, Baltimore. Contact Dr. Michael J. Asken, Chairperson, or Stephen Seitz, Coordinator, Sport Psychology Center of the Sheppard-Pratt Hospital System, P.O. Box 6815, Baltimore, MD 21285-6815; 1-800-627-0550.

OCTOBER

October 9–11, 2nd congress, World Association for Psychosocial Rehabilitation, Barcelona, Spain. Contact J.L. Marti-Tusquets, University of Barcelona, Casanova 143, Barcelona 08036, Spain.

October 10–14, 8th International Forum of Psychoanalysis, Rio de Janeiro, Brazil. Contact ADAM Congressos e Eventos Ltda., 63, Av. Almirante Barroso, Grps. 1413-1414, Rio de Janeiro 20031, R.J., Brazil; 021-220-2781.

October 11–15, annual meeting, American Academy of Child and Adolescent Psychiatry, New York. Contact Virginia Q. Anthony, Executive Director, 3615 Wisconsin Avenue, NW, Washington, DC 20016; 202-966-7300.

October 13–15, 6th International Conference on Multiple Personality/Dissociative States, Chicago. Contact Bennett G. Braun, M.D., Program Director, ICMP/DS, Rush-Presbyter-

(Continued on page A25)



Asleep at the switch. This calls for a switch in antidepressants.

With PAMELOR there is little daytime sedation.
Yet all the efficacy of amitriptyline.

When patients with depression are being treated with PAMELOR, they're able to keep operating on all circuits.

That's because PAMELOR works as effectively as amitriptyline,¹ yet doesn't keep your patient from working. Daytime sedation is low²⁻⁷; consequently, patient productivity can remain high.

What's more, PAMELOR has a low incidence of anticholinergic^{2,3,7} and hypotensive^{2,4,7-10} side effects. So, for those patients on another antidepressant, a switch to

PAMELOR therapy could help across the board.

PAMELOR may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating heavy machinery or driving a car; therefore, the patient should be warned accordingly. Because of anticholinergic activity, PAMELOR should be used with caution in patients who have glaucoma or a history of urinary retention. As with all antidepressants, patients

with cardiovascular disease should be given PAMELOR only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time.


PAMELOR[®]
(nortriptyline HCl)

The active metabolite of amitriptyline

For Brief Summary, please see following page.



PAMELOR[®]

(nortriptyline HCl)

The active metabolite of amitriptyline



All the efficacy of amitriptyline¹ and

- little daytime sedation²⁻⁷
- low incidence of orthostatic hypotension^{2-4,7-10}
- low incidence of anticholinergic side effects^{2,3,7}

References: 1. Ziegler VE, Clayton PJ, Biggs JT. A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry*. May 1977;34:607-612. 2. Thompson LL, Thompson WL. Treating depression: Tricyclics, tetracyclics, and other options. *Modern Medicine*. August 1993;51:87-109. 3. Georgoulas A. Affective disorders: pharmacotherapy. In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry IV*. Baltimore, Md: Williams & Wilkins, 1985;1821-833. 4. Blackwell B, Peterson GR, Kuzma RJ, Hostetter RM, Adolph AB. The effect of five tricyclic antidepressants on salivary flow and mood in healthy volunteers. *Communications in Psychopharmacology*. 1980;4:255-261. 5. Bye C, Clubley M, Peck AW. Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol*. 1978;6:155-161. 6. Kupfer DJ, Spiker DG, Rossi A, Coble PA, Shaw D, Ulrich R. Nortriptyline and EEG sleep in depressed patients. *Biol Psychiatry*. 1982;17:535-546. 7. Hayes PE, Kristoff CA. Adverse reactions to five new antidepressants. *Clin Pharm*. 1986;5:471-480. 8. Roose SP, Glassman AH, Siris SG, Walsh BT, Bruno RL, Wright LB. Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: a meaningful difference. *J Clin Psychopharmacol*. 1981;1:316-319. 9. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Gilman AG, Goodman LS, Rail TW, Murad F, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 7th ed. New York, NY: Macmillan Publishing Co., 1985;413-423. 10. Thaysen P, Bjerrre M, Kragh-Sorensen P, et al. Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology*. 1981;74:360-364.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor[®] (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor[®] (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time, myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such

as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher AUC, and lower clearance of nortriptyline.

Use in Pregnancy: Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children: Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension,

tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation, insomnia, panic, nightmares, hypomania, exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities, incoordination, ataxia, tremors, peripheral neuropathy, extensor pyramidal symptoms, seizures, alteration in EEG patterns, linnit. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis, blurred vision, disturbance of accommodation, mydriasis, constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (genital or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone marrow depression, including agranulocytosis, eosinophilia; purpura, thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peptic ulcer, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, impotence, testicular swelling, elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulated obstructive), altered liver function, weight gain or loss, perspiration, flushing, urinary frequency, nocturia, drowsiness, dizziness, weakness, fatigue, headache, parotid swelling, alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congest heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

(PAM-217—1/13/7)



Dorsey Division
SANDOZ PHARMACEUTICAL
Corporation, E. Hanover, NJ 07936 (201) 503-7500

Take a close look at Quality.



FLUPHENAZINE HCl TABLETS

1mg/2.5mg/5mg/10mg

Now Available from Bolar
For Immediate Delivery...
The Bolar Generic for Prolixin®

 **BOLAR**
Pharmaceutical Co., Inc.
MANUFACTURERS OF GENERIC PHARMACEUTICALS

33 Ralph Avenue, P.O. Box 30
Copiague, NY 11726-0030
Phone: (516) 842-8383 Fax: (516) 842-8630
Manufacturing facilities located in:
Copiague, New York • Humacao, Puerto Rico

Bioavailability information available upon request.
Prolixin is a registered trademark of Princeton Pharmaceutical Products (A Squibb Company)



Emergency medicine.

Management of severely disruptive behavior: Ativan® Injection with a neuroleptic.

Rapid tranquilization with a wider margin of safety.

Although neuroleptic agents provide an effective means of controlling violent or destructive behavior, their use is associated with a risk of serious and potentially irreversible adverse effects.¹⁻² Dose reduction is the best way to minimize this risk, but such a solution may not be possible during an emergency. The use of ATIVAN Injection combined with a low-dose neuroleptic provides an alternative pharmacologic approach for sedating anxious and agitated patients exhibiting severely disruptive behavior.

Clinical experience with this combination suggests that effective

control can be achieved with lower neuroleptic doses than when using a neuroleptic alone.³

Ativan® Injection: Pharmacologically desirable as an adjunct for sedation.

Unlike other benzodiazepines, ATIVAN Injection is readily absorbed following intramuscular administration,⁴ with peak plasma concentrations occurring in approximately 60 to 90 minutes.⁵ Mean half-life is about 16 hours and the desired sedative and anxiolytic effects usually last 6 to 8 hours.^{5*}

*The additive central-nervous system effects of neuroleptics should be borne in mind when used concomitantly with ATIVAN Injection.

Please see the adjacent page for a brief summary of prescribing information.

Ativan® Injection I.M. (lorazepam)

**Calm the patient,
curtail adverse reactions.**

ATIVAN® INJECTION I.M. (LORAZEPAM) Ⓞ

DESCRIPTION: Ativan® (lorazepam) Injection, a benzodiazepine with anxiolytic and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(6-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative. **CLINICAL PHARMACOLOGY:** IV or IM administration of recommended dose of 2 to 4 mg lorazepam injection to adult patients is followed by dose-related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery. In most patients, the clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15 to 20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6 to 8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of morphine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse (See WARNINGS and ADVERSE REACTIONS).

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8 to 10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults — for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients endoscopy and/or surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation (See WARNINGS).

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASICATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide) is renal, lorazepam is not recommended in hepatic and/or renal failure. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

PREGNANCY: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlorazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibiae, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g., phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection (See CLINICAL PHARMACOLOGY and WARNINGS). Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE AND ADMINISTRATION). When lorazepam is used IV as premedication prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose (See ADVERSE REACTIONS).

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g., sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedication that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers and narcotic or analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 8 to 8 hours after surgery.

Laboratory Tests: In clinical trials, no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, drug acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g., narcotic analgesics, inhalation anesthetics, scopolamine, atropine and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during a 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility. **Pregnancy:** Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE AND ADMINISTRATION). On rare occasions (3/1580), patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (either seen most commonly when scopolamine given concomitantly as premedication). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.5% immediately postinjection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 15/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary under-ventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

BROSE ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over a prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypoxia, stages one to three coma and, very rarely, death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injections: For designated indications as premedication, usual IM doses of lorazepam are 0.05 mg/kg up to maximum of 4 mg. As with all premedications, individualize dose (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS). Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS). For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure. Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injections: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses — as high as 0.05 mg/kg up to total of 4 mg — may be given (See CLINICAL PHARMACOLOGY, WARNINGS and ADVERSE REACTIONS). Doses of other injectable CNS depressants should ordinarily be reduced (See PRECAUTIONS). For optimum effect, measured as lack of recall, IV lorazepam should be administered 15 to 20 minutes before anticipated operative procedure.

EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (See WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP; Sodium Chloride Injection, USP; 5% Dextrose Injection, USP.

BOW SUPPLIES: Ativan® (lorazepam) Injection, Wyeth, is available in single- and multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 1 ml and 10 ml vials and 1 ml fill in 2 ml TUBEX.

4 mg/ml, NDC 0008-0570; 1 ml and 10 ml vials and 1 ml fill in 2 ml TUBEX.

For IM or IV Injection. Protect from light. Keep in refrigerator.

Directions for Injection for IV Use: To dilute, adhere to following procedure: For TUBEX — (1) Extract entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogeneous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial — Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

CI 3261-2

6/22/83

References:

- Gruhnman R, Günter W, Rütter E. Adverse effects of psychotropic drugs. In: Hippel H, Winkler G (eds): *Clinical Psychopharmacology*. Amsterdam: Excerpta Medica, 1983, pp 378-385.
- Dubin WR: Rapid tranquilization: Antipsychotics or benzodiazepines? *J Clin Psychiatry* 1988;49(suppl):5-11.
- Sabzan C, Green AL, Rodriguez-Villa F, et al: Benzodiazepines combined with neuroleptics for management of severe disruptive behavior. *Psychosomatics* 1986;27(suppl):17-21.
- Harvey SC: Hypnotics and sedatives. In Gilman AG, Goodman LS, Rall TW, et al (eds): *The Pharmacological Basis of Therapeutics*, ed 7. New York: Macmillan Publishing Company, 1985, pp 339-371.
- Data on file, Wyeth-Ayerst Laboratories.

**WYETH-AYERST
LABORATORIES**
Philadelphia, PA 19101

© 1989, Wyeth-Ayerst Laboratories

Calendar

(Continued from page A18)

rian-St. Luke's Medical Center, 6130 North Sheridan Road, Chicago, Illinois 60660; 312-508-6440 or 508-6442.

October 13-19, 8th World Congress of Psychiatry, World Psychiatric Association, Athens, Greece. Contact Dr. Constantin R. Soldatos, Department of Psychiatry, Eginition Hospital, 74 Vassilissis Sophias Avenue, Athens 11528 Greece; 30 1 72 23 670.

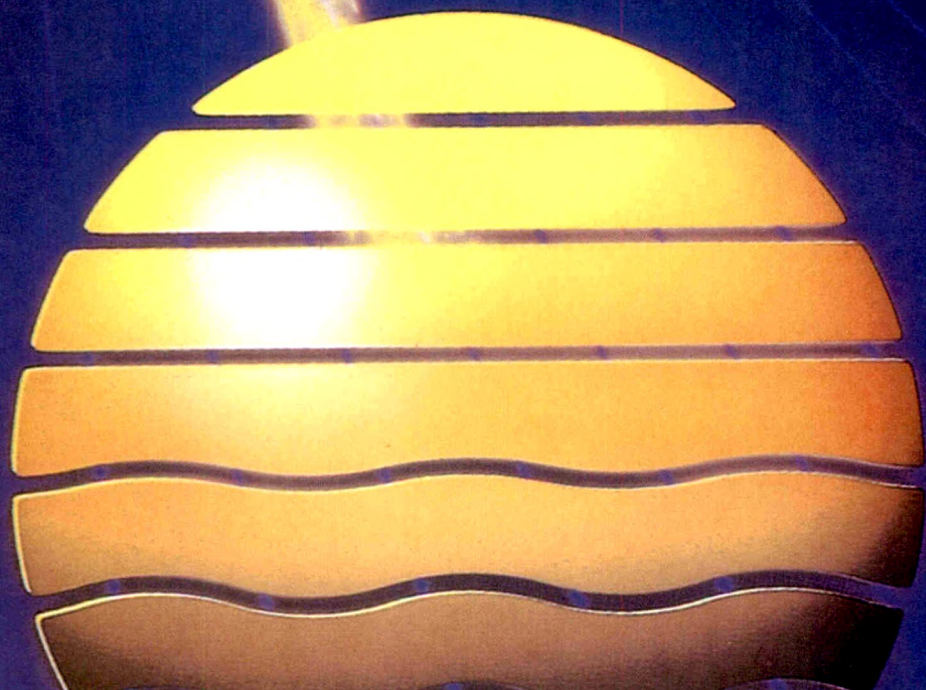
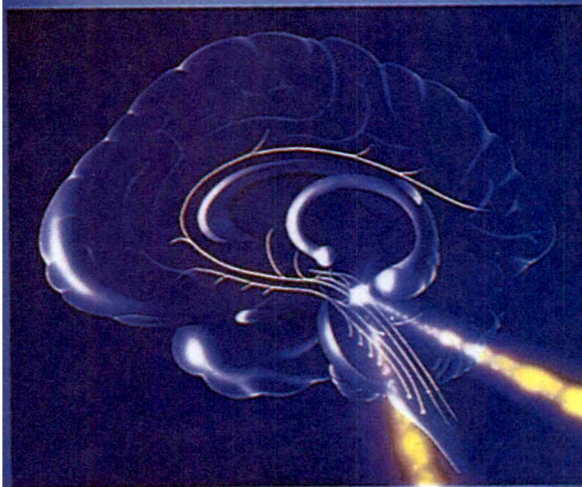
October 18-21, annual meeting, American Academy of Clinical Psychiatrists, St. Louis. Contact Alicia A. Muñoz, Executive Secretary, P.O. Box 3212, San Diego, CA 92103; 619-298-4782.

October 19-22, annual meeting, American Academy of Psychiatry and the Law, Washington, D.C. Contact Jonas R. Rapoport, M.D., Medical Director, 1211 Cathedral Street, Baltimore, MD 21201; 301-539-0379.

October 26-29, 47th annual conference, American Association for Marriage and Family Therapy, San Francisco. Contact AAMFT, Department C, 1717 K Street, NW, #407, Washington, DC 20006; 202-429-1825.

October 26-29, annual meeting, Academy of Psychosomatic Medicine, Las Vegas. Contact Evelyn Hallberg, Executive Director, 5824 N. Magnolia, Chicago, IL 60660; 312-784-2025.

The synapse—crossroads for serotonin



In depression

PROZAC[®]

fluoxetine hydrochloride

**a potent serotonin reuptake inhibitor...
represents a new class
of antidepressants”¹**

Effectively relieves depression*

Unlike the tricyclics, Prozac specifically inhibits serotonin uptake. Its minimal action on other neurotransmitters may explain its favorable side-effect profile.

Fewer side effects to disrupt therapy

Side effects are generally mild and manageable, and include nausea, anxiety/nervousness, insomnia, and drowsiness

Avoid using MAO inhibitors concomitantly or in proximity to Prozac

Rash and/or urticaria occurred in 4% of clinical trial patients

A wide margin of safety

20-mg once-a-day therapy

PROZAC...
**A specifically different
antidepressant**



1. *Curr Ther Res* 1986;39:559-563.
*As defined by DSM-III.

*See adjacent page
for brief summary of
prescribing information.*

Prozac®

fluoxetine hydrochloride

Brief Summary: Consult the package literature for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindication: Prozac is contraindicated in patients known to be hypersensitive to it.

Warnings: Monoamine Oxidase Inhibitors—Data on the effects of the combined use of fluoxetine and MAOI inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAOI inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of fluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgia, edema, facial edema, respiratory distress, lymphadenopathy, prothrombin, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknown at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: General—Anxiety and Insomnia—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately double that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo and 3% of tricyclic antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see Clinical Pharmacology and Dosage and Administration).

Use in Patients With Concomitant Illness—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism of concomitant medications.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect their ability.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected. Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests—There are no specific laboratory tests recommended.

Drug Interactions—As with all drugs, the potential for interaction by a variety of mechanisms (i.e., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility (see Accumulation and Slow Elimination under Clinical Pharmacology).

Tryptophan—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors—See Warnings.

Other Antidepressants—There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (see Accumulation and Slow Elimination under Clinical Pharmacology).

Discontinuation—The half-life of concurrently administered diazepam may be prolonged in some patients (see Accumulation and Slow Elimination under Clinical Pharmacology).

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, diazepam) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (see Accumulation and Slow Elimination under Clinical Pharmacology).

CNS-Active Drugs—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (see Accumulation and Slow Elimination under Clinical Pharmacology).

Epileptomimetic Therapy—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children—Safety and effectiveness in children have not been established.

Usage in the Elderly—Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have comorbid or systemic illnesses or who are receiving concomitant drugs.

Hypotension—Several cases of hypotension (a syncopal attack with serum sodium lower than 110 mEq/L) have been reported. The hypotension appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Adverse Reactions: Commonly Observed—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The most common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.6%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

TABLE 1. TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event		Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Prozac (N=1,730)	Placebo (N=789)		Prozac (N=1,730)	Placebo (N=789)
Nervous			Body as a Whole		
Headache	20.3	16.5	Anxiety	4.4	1.9
Nervousness	14.9	8.5	Insomnia	3.4	3.1
Insomnia	13.8	7.1	Pain, limb	1.6	1.1
Drowsiness	11.6	8.5	Fatigue	1.5	1.1
Depression	7.9	2.4	Chest pain	1.2	1.1
Tremor	6.7	3.3	Allergy	1.2	1.1
Dizziness	4.2	1.1	Intoxication	1.2	1.5
Fatigue	4.2	1.1			
Sweating	1.8	1.3	Respiratory		
Cardiovascular			Upper		
Palpitations	1.7	2.0	Respiratory		
Libido, decreased	1.6	—	Infection	7.6	6.0
Lightheadedness	1.6	—	Flu-like		
Concentration, decreased	1.5	—	Symptoms	2.8	1.9
			Pharyngitis	2.7	1.3
			Congestion	2.6	2.3
Digestive			Nausea	2.3	1.8
Nausea	21.1	10.1	Stomatitis	2.1	2.0
Diarrhea	12.3	7.0	Cough	1.6	1.8
Mouth			Dyspepsia	1.4	—
Erythema	9.5	8.0			
Anorexia	7.7	1.5	Cardiovascular		
Dyspepsia	6.4	4.3	Hot flashes	1.8	1.0
Constipation	4.5	3.3	Precipitation	1.3	1.4
			Musculoskeletal		
			Pain, back	2.0	2.4
			Pain, foot	1.2	1.1
			Pain, muscle	1.2	1.0
			Genitourinary		
			Menstruation, irregular	1.9	1.4
			Sexual		
			Dyspareunia	1.9	—
			Frequent		
			Urination	1.6	—
			Urinary tract		
			Infection	1.2	—
			Special Senses		
			Vision		
			Disturbance	2.8	1.8

*Events reported by at least 1% of Prozac-treated patients are included.
—Incidence less than 1%.

Incidence in Controlled Clinical Trials—Table 1 enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigations. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

Other Events Observed During the Premarketing Evaluation of Prozac—During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Unwanted events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without the grouping similar types of unwanted events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited on at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole—Frequent: chills; infrequent: chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; Rare: adenoid enlarged, cellulitis, hydrocephalus, hypohidrosis, Li syndrome, moniliasis, and serum sickness.

Cardiovascular System—Infrequent: angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; Rare: AV block (first-degree), bradycardia, bundle-branch block, cerebral ischemia, myocardial infarction, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System—Frequent: increased appetite; infrequent: aphthous stomatitis, flatulence, gastritis, glossitis, epigastric pain, glossitis, liver function tests abnormal, melena, stomatitis, and thrush; Rare: bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System—Infrequent: hypothyroidism; Rare: goiter and hyperthyroidism.

Hemic and Lymphatic System—Infrequent: anemia and lymphadenopathy; Rare: bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechiae, purpura, sedimentation rate increased, and thrombocytopenia.

Metabolic and Nutritional—Frequent: weight loss; infrequent: generalized edema, hypoglycemia, peripheral edema, and weight gain; Rare: dehydration, gout, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, hypoproteinemia, hypotension, and iron deficiency anemia.

Musculoskeletal System—Infrequent: arthralgia, bone pain, burr-like tenosynovitis, and twitching; Rare: bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatic arthritis.

Nervous System—Frequent: abnormal dreams and agitation; infrequent: abnormal gait, acute brain syndrome, ataxia, amnesia, apathy, ataxia, bulbar palsy, cerebellar ataxia, CNS stimulation, convulsion, delirium, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperreflexia, hyperesthesia, incoordination, libido increased, manic reaction, neuritis, neuropathy, paranoid reaction, psychosis, and vertigo; Rare: abnormal electroencephalogram, arthralgia, ataxia, chronic brain syndrome, circumscribed chorea, CNS depression, coma, convulsion, dyskinesia, extrapyramidal syndrome, hyperreflexia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and vertigo.

Respiratory System—Frequent: bronchitis, rhinitis, and yawn; infrequent: asthma, epistaxis, hiccup, hyperventilation, and pneumonia; Rare: apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/atelectasis, and pleural effusion.

Skin and Appendages—Infrequent: acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; Rare: eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, perioritis, purpura, rash, pustular rash, seborrhea, skin discoloration, skin hyper trophy subcutaneous nodules, and vesiculobullous rash.

Special Senses—Infrequent: amblyopia, conjunctivitis, ear pain, eye pain, myopia, photophobia, and tinnitus; Rare: buphthalmos, cataract, cornea lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System—Infrequent: abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urinary impairment, and vaginitis; Rare: abortion, abnormal menses, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postproduction Reports—Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after drug withdrawal, hyperprolactinemia, and thrombocytopenia.

Overdosage: Human Experience—As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of meprobamate. Plasma concentrations of fluoxetine and meprobamate were 4.67 mg/L and 4.18 mg/L, respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine 1.83 mg/L; norfluoxetine, 1.10 mg/L; citalopram, 1.80 mg/L; temazepam, 3.81 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (see Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent symptoms of overdose including agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without sequelae.

PY 2472 DFP

(11/17/88)

Additional information available to the profession on request from



Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46285

Prozac® (fluoxetine hydrochloride, Dista)

Diagnostic Edge.



The Cadwell Spectrum 32. More objectivity in psychiatric diagnoses.

As new technologies provide more insight into brain function, psychiatry is integrating more objective data into diagnosis. The Cadwell Spectrum 32 Neurometric Analyzer provides the most comprehensive evaluation of brain electrical activity available. And gives you the diagnostic edge in corroborating a number of psychiatric disorders.

Neurometrics provides accurate differentiation.

The Spectrum 32 samples brain activity from multiple scalp locations simultaneously. Then through a process called "neurometrics," it extracts objective features and statistically evaluates these measurements relative to a normative database to detect abnormalities.



The Neurometric Analyzer goes beyond merely identifying a problem. It compares the patient's EEG profile to those of a variety of disorders, extracted from the Neurometric Psychiatric Database of more than 5000 evaluations. Then it calculates the probability that the patient's profile corresponds to profiles characteristic of: Learning Disabilities, Alcoholism, Dementia (Vascular vs. Non Vascular), Multiple Infarct Dementia, and Major Depression (Unipolar vs. Bipolar).

An objective adjunct to clinical diagnosis.

The Spectrum 32 provides invaluable, accurate insights into brain dysfunctions. Although it does not replace clinical diagnosis, it *does* give you objective data presented in numerical

tables, waveforms and topographic maps to support your clinical conclusions. And to help you evaluate response to treatment more precisely.

With the Spectrum 32 you not only can evaluate your own patients with new objectivity, you can also provide a referring lab service for your colleagues. Quantitative EEG measurements can be taken quickly by an EEG technologist, so you can add this service without taking too much time away from your current patients.

More than "how-to" training.

In addition to courses on neurometrics and brainmapping, Cadwell offers marketing expertise and reimbursement information. Everything you need to help you make the system *economically* — as well as *clinically* — viable.

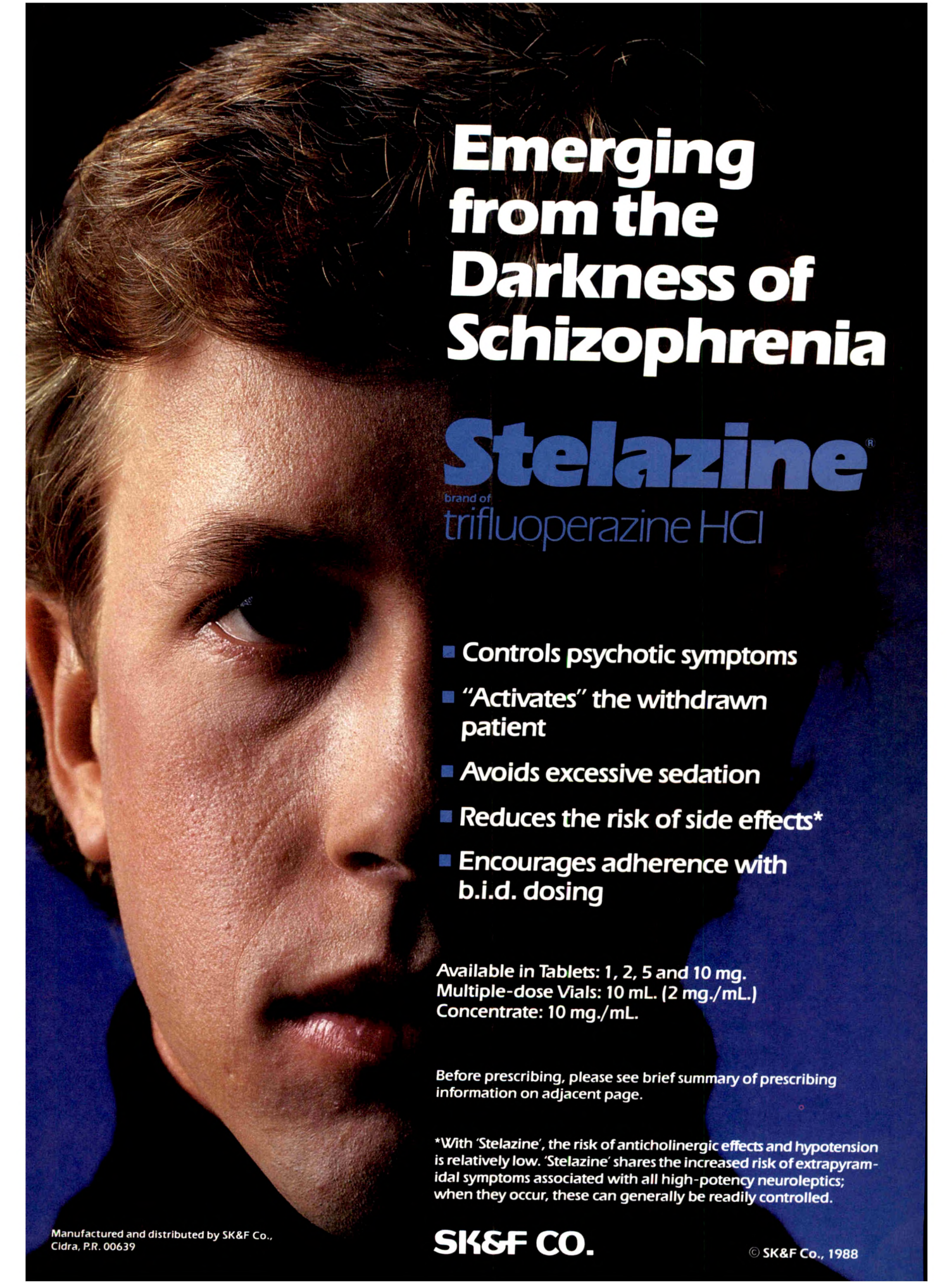
Find out how the Spectrum 32 can give you the diagnostic edge. And how it can brighten your practice's financial picture. Call 1-800-678-6655 or 509-735-6481.

Your Clinical Link To Advanced Technology

CADWELL®

Books Received

- The Development of Children**, by Michael Cole and Sheila R. Cole. New York, Scientific American Books (W.H. Freeman and Co., distributor), 1989, 678 pp., \$36.95.
- Depression After Childbirth: How to Recognize and Treat Postnatal Illness**, 2nd ed., by Katharina Dalton. New York, Oxford University Press, 1989, 161 pp., \$10.95 (paper).
- Anorexia Nervosa and Other Dyscontrol Syndromes**, by E.L. Edelstein. New York, Springer-Verlag, 1989, 114 pp., \$35.00.
- Handbook of Geriatric Assessment**, by Joseph J. Gallo, M.D., William Reichel, M.D., and Lillian Andersen, R.N., Ed.D. Rockville, Md., Aspen, 1988, 220 pp., \$29.50.
- The Essential Partnership: How Parents and Children Can Meet the Emotional Challenges of Infancy and Childhood**, by Stanley I. Greenspan, M.D., and Nancy Thorndike Greenspan. New York, Viking, 1989, 250 pp., \$18.95.
- The Dance of Intimacy: A Woman's Guide to Courageous Acts of Change in Key Relationships**, by Harriet Goldhor Lerner, Ph.D. New York, Harper & Row, 1989, 244 pp., \$17.95.
- Victims No Longer: Men Recovering From Incest and Other Sexual Child Abuse**, by Mike Lew. New York, Nevraumont, 1988, 393 pp., \$19.95.
- Clinical Physiology of Sleep**, edited by Ralph Lydic and Julien F. Biebuyck. Bethesda, Md., American Physiological Society (New York, Oxford University Press, distributor), 1988, 228 pp., \$49.00.
- Foundations of Object Relations Family Therapy**, edited by Jill Savege Scharff, M.D. Northvale, N.J., Jason Aronson, 1989, 478 pp., no price listed.
- In Bad Taste: The MSG Syndrome**, by George R. Schwartz, M.D. Santa Fe, N.Mex., HealthPress, 1988, 111 pp., \$14.95.
- Surviving an Eating Disorder: New Perspectives and Strategies for Family and Friends** (1988), by Michele Siegel, Ph.D., Judith Brisman, Ph.D., and Margot Weinshel, M.S.W. New York, Perennial Library (Harper & Row), 1989, 216 pp., \$8.95 (paper).
- Health Psychology and Public Health: An Integrative Approach**, by Richard A. Winett, Abby C. King, and David G. Altman. Oxford, Pergamon Press, 1989, 422 pp., \$49.50; \$22.50 (paper).
- The Seat of the Soul**, by Gary Zukav. New York, Simon & Schuster, 1989, 248 pp., \$17.95.



Emerging from the Darkness of Schizophrenia

Stelazine[®]
brand of
trifluoperazine HCl

- Controls psychotic symptoms
- "Activates" the withdrawn patient
- Avoids excessive sedation
- Reduces the risk of side effects*
- Encourages adherence with b.i.d. dosing

Available in Tablets: 1, 2, 5 and 10 mg.
Multiple-dose Vials: 10 mL (2 mg./mL.)
Concentrate: 10 mg./mL.

Before prescribing, please see brief summary of prescribing information on adjacent page.

*With 'Stelazine', the risk of anticholinergic effects and hypotension is relatively low. 'Stelazine' shares the increased risk of extrapyramidal symptoms associated with all high-potency neuroleptics; when they occur, these can generally be readily controlled.

Stelazine®

brand of
trifluoperazine HCl

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

SK&F CO.

Manufactured and distributed by
SK&F Co., Cidra, P.R. 00639

BRS-SZ-L63

© SK&F Co., 1988

INTELLIGENT ECT FROM MECTA CORP. UL LISTED CSA CERTIFIED MODULAR AND COMPUTERIZED

SR-1



JR-1



FLEXIBILITY



PRINTED SELF TEST AND TREATMENT RESULTS

ADDITIONAL FEATURES INCLUDED WITH ALL SR MODELS ARE:

- EEG instrumentation amplifier
- Built-in 2 channel digital chart recorder
- Numeric timing marks during monitoring
- Printed record of energy level
- Printed date and time of treatment
- ECG instrumentation amplifier
- Selectable single or dual channel
- Printed record of treatment and self test
- Printed record of stimulus parameters
- Modular design for maximum flexibility

SR/JR FEATURES INCLUDE:

- Continuous reading of energy in Joules
- Tilttable Liquid Crystal Display
- Bi-polar brief pulse stimulus
- Adjustable constant current stimulus
- Audible warning prior to treatment
- Remote control capabilities
- 100% expected seizure induction
- Totally isolated for maximum safety
- Single or multiple energy control(s)
- All parameters displayed in text form
- Increased energy for difficult cases
- Built-in self test for patient safety
- Steady warning tone during treatment
- Protected STIMULUS CONTROL push button
- Timing accuracy better than .1%
- 1 year parts and labor warranty
- Operates on 120 or 240 VAC
- Complete with all accessories

SR-2



JR-2



SINGLE ENERGY LEVEL CONTROLS

SIMPLICITY

MECTA Corporation 5622 SW Kelly Street Portland, OR 97201 (503) 245-6975



ECONOMICS OF SCIENTIFIC JOURNALS

"This publication is an in-depth source for anyone who wants to learn about the inner workings of scientific journal publishing. Although it deals mostly with society, not-for-profit publishing, it provides the reader with the general philosophy and methods used by most commercial publishers as well."

--Society for Scholarly Publishing Letter

CONTENTS: Member Subscriptions • Single Issues and Back Volumes • Reprints • Advertising in Scholarly Journals • Page Charges • Journal Income: a Multipublisher's View • Editorial Operations • Copy Editing • Purchasing Typesetting Separately from Printing • Presswork, Binding, and Paper • Distribution and Postage • Subscription Fulfillment • Budgeting, Accounting, and Financial Planning • Marketing the Scientific Journal • Subject Index

Paperbound; ISBN: 0-914340-03-4; Publication date: December 1982; Trim size: 6 x 9 inches; 106 pages

Regular Price: \$11.95 (10% discount on 10 or more copies delivered to one address)

CBE Member Discount Price: \$10.75 (single copy paid by personal check)

Terms of Sale: All sales final; no returns.

Prepayment required; U.S. currency drawn on a U.S. bank.

Price includes BOOK RATE postage.

For faster delivery--first class, air mail, or UPS available at additional charge (book weight 8.5 oz).

Maryland residents, please add 5% sales tax.

COUNCIL OF BIOLOGY EDITORS, INC.
9650 Rockville Pike, Bethesda, MD 20814

When Psychotic Features Complicate Depression **Simplify Therapy With a Single Agent**

ASENDIN improved the condition of 86% of depressed patients with psychotic features, based on the Brief Psychiatric Rating Scale (BPRS)¹

Simple, easy-to-follow dosage schedule

Suggested dosage in depression with psychotic features is 100 mg bid. Adjust according to clinical response and tolerance*

Hallucinations

Delusions

Ruminations

*ASENDIN may be given in a single daily dose, not to exceed 300 mg, preferably at bedtime. If the total daily dosage exceeds 300 mg, it should be given in divided doses.

ASENDIN inhibits reuptake of norepinephrine and serotonin and also has dopamine-blocking activity which may be associated with neuroleptic side effects, including tardive dyskinesia, in some patients. Please see brief summary of prescribing information on adjacent page, especially **Warnings** and **Information for the Patient** sections.



ASENDIN
amoxapine

Brief Summary
ASENDIN® amoxapine Tablets
 25 mg, 50 mg, 100 mg, 150 mg

CLINICAL PHARMACOLOGY

ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is not well understood. In animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of dopamine receptors to dopamine. Amoxapine is not a monoamine oxidase inhibitor.

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. *In vitro* tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occur within 2 weeks in over 80% of responders.

INDICATIONS

ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.

CONTRAINDICATIONS

Prior hypersensitivity to benzazepine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hypertensive crisis, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN allow a minimum of 14 days to elapse, then initiate cautiously, with gradual increase in dosage until optimum response is achieved.

WARNINGS

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (i.e., antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substantial neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is important to be alert to the possibility of its development at any age. The onset of tardive dyskinesia, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely. If neuroleptic treatment is withdrawn, neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptic, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for the Patient and ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex, NMS has been reported in association with antipsychotic drugs. Clinical manifestations are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Diagnosis is complicated. Rule out serious medical illness (e.g., pneumonia, systemic infection) and inadequately treated extrapyramidal symptoms (EPS). Other considerations in differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology. Management of NMS includes immediate discontinuation of antipsychotic and other drugs not essential to current therapy, intensive symptomatic treatment and medical monitoring, and treatment of concomitant serious medical problems for which specific treatments are available. Reintroduction of antipsychotic drug treatment after recovery from NMS should be carefully considered and closely monitored since recurrences of NMS have been reported.

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS

General: Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN amoxapine should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in <1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported. Information for the Patient: It is advised that all patients with history of neuroleptic treatment be given full information about the risk of tardive dyskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired. **Drug Interactions:** See **CONTRAINDICATIONS** regarding concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when amitriptyline is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered. **Therapeutic Interactions:** Concurrent administration with electroconvulsive therapy may increase hazards associated with such therapy. **Cardiotoxicity:** Impairment of fibrillatory in a 24-month toxicologic study in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length. **Pregnancy:** Pregnancy Category C: Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryofetotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-6) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women. **Pediatric Use:** Safety and effectiveness in children below the age of 16 have not been established.

ADVERSE REACTIONS

Reported in Controlled Studies: Incidence Greater than 1%: Most frequent were sedative and anticholinergic: drowsiness (44%), dry mouth (44%), constipation (22%), and blurred vision (7%). Less frequently: CNS and Neuromuscular: anxiety, insomnia, restlessness, nervousness, palpitations, tremor, confusion, excitement, nightmares, dizziness, alterations in EEG patterns. Allergic: edema, skin rash. Endocrine: elevation of prolactin levels. Gastrointestinal: nausea, other: dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration. Incidence Less than 1%: Anticholinergic: disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness. Cardiovascular: hypotension, hypertension, syncope, tachycardia. Allergic: drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis. CNS and Neuromuscular: tingling, paresthesias of the extremities, tremor, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported. (See **WARNINGS**.) Hematologic: leukopenia, agranulocytosis. Gastrointestinal: epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea. Endocrine: increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion. Other: lacrimation, weight gain or loss, altered liver function, painful ejaculation. **Drug Relationship Unknown:** Reported rarely, but under circumstances where drug relationship was unknown: Anticholinergic: paralytic ileus. Cardiovascular: atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block. CNS and Neuromuscular: hallucinations. Hematologic: thrombocytopenia, eosinophilia, purpura, pterichiae. Gastrointestinal: parotid swelling. Endocrine: change in blood glucose levels. Other: pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, a dispepsia. **Additional Adverse Reactions:** Reported with other antidepressants with ASENDIN: Anticholinergic: anticholinergic toxicity, dilation of the urinary tract. CNS and Neuromuscular: delusions. Gastrointestinal: stomatitis, black tongue. Endocrine: gynecomastia.

OVERDOSE

Signs and Symptoms: Toxic manifestations of ASENDIN overdose differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures. The toxic effects of ASENDIN overdosage should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, if it develops, requires vigorous treatment such as that described by Delgado-Escueta, et al. (*N Engl J Med* 1982; 306:1337-1340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for non-drug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits, even in the presence of sinus tachycardia. Hence, prolongation of the QT interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients.

Rev. 11/87

1. Anton RE, Hiti A, Diamond BL, et al: Amoxapine treatment of psychotic depression: Dose effect and dopamine blockade. *J Clin Psychiatry Monograph* 1986;4:32-36.

LEDERLE LABORATORIES
 A Division of American Cyanamid Company
 Wayne, New Jersey 07090
 © 1989 Lederle Laboratories

6543-9



AMERICAN PSYCHIATRIC ASSOCIATION'S

CONSULTATION SERVICE

Could you use the APA's assistance in planning, improving services or solving a problem at your hospital or facility?

This long-standing program of the APA provides confidential consultations to all mental health care organizations on topics ranging from low utilization of beds to disagreement among staff about methods of treatment.

We will provide a focused consultation tailored to meet your specific needs. Our professional consultants are outstanding psychiatrists and experts in other related disciplines. Our reasonable fees make the Consultation Service a cost-effective way to help resolve your organization's problems.

For more information contact

Ms. Susan Kupe
 Consultation Service
 American Psychiatric Association
 1400 K Street, N.W.
 Washington, DC 2000
 (202) 682-620

All inquiries remain confidential.

The only journal providing a complete and systematic review of the entire field

Complete Coverage

Each issue provides a complete and systematic review of the past year's developments in one or two sections of psychiatry. Together the six bimonthly issues cover the entire field of psychiatry.

Annotated References

In each review, the author selects and annotates the author's most significant papers on that topic, highlighting the key findings.

HUGH L. FREEMAN and DAVID J. KUPFER, Editors

Editorial Board

J Angst	AM Freedman	MH Lader	HY Meltzer	T Okuma
GB Cassano	MG Gelder	CA León	HG Morgan	G Parker
TJ Crow	H Katschnig	JJ López-Ibor Jr	PE Mullen	E Strömberg
L Eisenberg	S Kellam			

Section Editors

S Agras	JRM Copeland	JS Madden	AR Nicol	D Tantam
GE Berrios	J Davis	FJ Menolascino	JAO Russell	PJ Taylor
S Bloch	JFW Deakin	E Miller	ACP Sims	G Tischler
J Borus	B Harry			

Authoritative Reviews

Each section consists of a series of short, highly-illustrated reviews. Using a comprehensive bibliography, leading experts evaluate all new findings in their fields.

World Bibliography

In each issue, the bibliography of current world literature lists all relevant papers published in the past year.

It is specially compiled by psychiatrists from over 200 journals.

Volume 2 Number 1 February 1989

Psychoses

edited by J.M. Davis

J.M. Davis	Editorial overview
K.A. Busch	Psychotic states in human immunodeficiency virus illness
P.G. Janicak	Recent advances in the assessment and treatment of psychotic affective disorders
A. Tamminga and G.K. Thaker	Tardive dyskinesia
P.N. Sakkas	Neuroleptic malignant syndrome
L.S. Grossman, D.J. Luchins and M. Harrow	Positive and negative symptoms and the neurology of schizophrenia
S. Matthysse	Genetics of schizophrenia
D.L. Garver	Schizophrenia spectrum
I.A. Flaherty and K.M. Hoskinson	Cross-cultural research on schizophrenia and depression
E.S. Gershon	Genetics of manic-depressive illness
S.C. Schulz	Clinical schizophrenia: treatment, prognosis and syndromes
R. Sharma	Atypical antipsychotics
J.M. Davis	Psychoses: miscellaneous conditions

Neurosciences and neuropsychiatry

edited by J.F.W. Deakin

J.F.W. Deakin	Editorial overview
S.L. Handley	New directions in benzodiazepine research
R. Abrams	Electroconvulsive therapy
R.G. Morris	Neuropsychological aspects of dementia
S.W. Brown	Neuropsychiatry of epilepsy

Advances in the assessment and treatment of psychotic affective disorders Janicak

Inpatients as well as outpatients may be related to the findings of this large literature review.	severe depression. Mood incongruent delusions predicted a good response to ECT.
ANDRIUKAITIS S. et al. Psychotic depression. <i>J Clin Psych</i> 1988, 47:1-10.	11. ARONSON TA, SHUKLA S, GUJARVARTY K, HOFF A, DIBUONO M, KHAN E: Relapse in delusional depression — a retrospective study of the course of treatment. <i>Compr Psychiatry</i> 1988, 29:12-21.
Depressed inpatients and outpatients. A comprehensive review of the literature. A comprehensive review of the literature.	Studied relapse rate in 52 delusional depressives over an average of 32 months follow-up. Overall, the relapse rates were quite high (87%). Discontinuation on tapering off of neuroleptics during the first 12 months was associated with the majority of relapses during that period.
Relapse rates in outpatients.	12. JANICAK PG, BRESNAHAN DB, SHARMA R, DAVIS JM, COMATY JE, MALINICK C: A comparison of thiothixene with chlorpromazine in the treatment of mania. <i>J Clin Psychopharmacol</i> 1988, 8:33-37.

29 acute manic patients were randomly assigned to receive a low dose of

Current Opinion in PSYCHIATRY

Review articles · Recommended reading
Bibliography of the world literature

Vol 2 · 1989 · No 1

No 1	THIS ISSUE	February
	Psychoses · J Davis	
	Neurosciences and neuropsychiatry · JFW Deakin	
No 2	Neuroses and personality disorders Social psychiatry and rehabilitation	April
No 3	Psychotherapy and psychoanalysis, Substance misuse	June
No 4	Child and adolescent psychiatry, Psychogeriatrics	August
No 5	Mental retardation History, philosophy and economics of psychiatry	October
No 6	Forensic psychiatry, Behavioral sciences	December

CS
CURRENT
SCIENCE

distinctions other than in treatment response exist between psychotic and non-psychotic affective disorders.

Current world literature: Psychoses

GREEN AR: The mechanism of action of antidepressant treatments: basic aspects. <i>Pharmacopsychiatry</i> 1988, 21:3-5.	with a schizophrenic woman. <i>J Nerv Ment Dis</i> 1987, 175:575.
GREENFIELD D: Feigned psychosis in a 14-year-old girl. <i>Hosp Community Psychiatry</i> 1987, 38:73-74.	HYER L, GOUNEIA I, HARRISON WR, WARSJAW J, COUTSOURIDES: Depression, anxiety, paranoid reactions, hypochondriasis, and cognitive decline of later-life inpatient. <i>Gerontol</i> 1987, 42:92-94.
GROF E, HAAG M, GROF P, HAAG H: Lithium response and the sequence of episode polarities: preliminary report on a Hamilton sample. <i>Prog Neuropsychopharmacol Biol Psychiatry</i> 1987, 11:199-204.	IERODAKONOU CS, IACONIDES A: Somatic manifestations of depressive patients in different psychiatric settings. <i>Psychopathology</i> 1987, 20:136-143.
GROSS RA, HERRIDGE P: A manic-like illness associated with right frontal arteriovenous malformation. <i>J Clin Psychiatry</i> 1988, 49:119-120.	JANICAK PG, BRESNAHAN DB, SHARMA R, DAVIS JM, COMATY JE, MALINICK C: A comparison of thiothixene with chlorpromazine in the treatment of mania. <i>J Clin Psychopharmacol</i> 1988, 8:33-37. [12].
GROVE WM, ADRIANSEN NC, YOUNG M, ENDICOTT J.	JANICAK PG, PANDEY GN, DAVIS JM, BOSHER RA.

Call TOLL FREE: (800) 552-5866 or in PA call (215) 790-2279

PA689

Current Opinion in PSYCHIATRY, Volume 2, 1989 (6 issues)

P609

☐ Yes! Please enter my Personal Subscription \$100.

☐ Institutional Subscription \$135.

Payment Method: ☐ Check enclosed, payable to Current Science

☐ Bill me ☐ VISA ☐ Mastercard ☐ American Express

Card Number _____ Exp. _____

Signature _____ Date _____

Money-Back Guarantee: If not completely satisfied with this journal, you may cancel your subscription by writing to Current Science within 30 days of receiving the first issue. Your payment will be fully refunded.

Name _____

Address _____

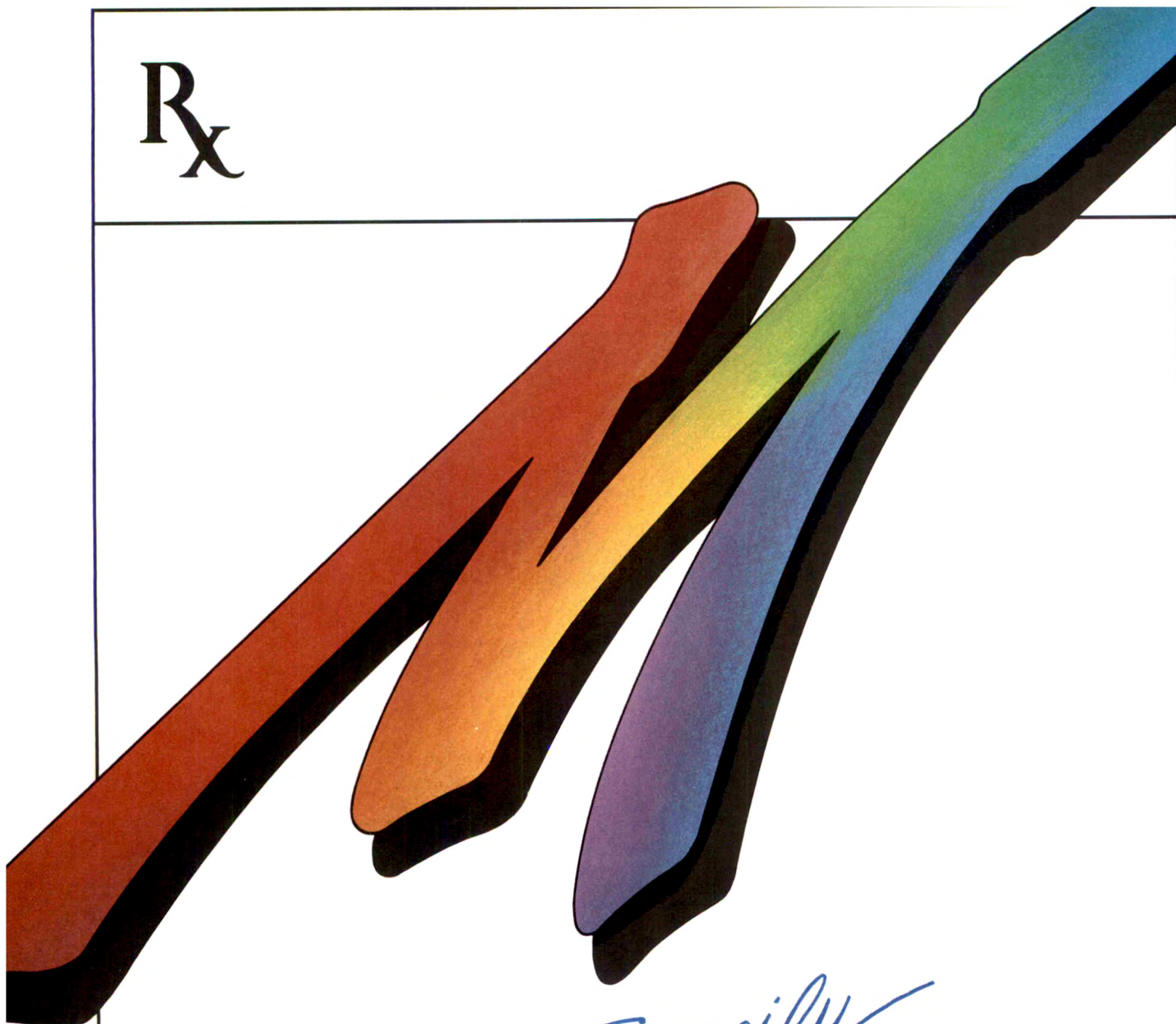
City/State/Zip _____

MAIL TO:

CS
CURRENT
SCIENCE

CURRENT SCIENCE
DEPARTMENT PA
1201 LOCUST STREET
PHILADELPHIA, PA 19107-9824

R_x



Protect Your Prescription *Specify* Dispense as Written

Mellaril[®]
(thioridazine)



Dorsey Division
SANDOZ PHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

© 1987 Sandoz Pharmaceuticals Corporation

MEL-887-1



10 mg



15 mg



25 mg



50 mg



100 mg



150 mg



200 mg



30 mg/ml



100 mg/ml



25 mg/5 ml



100 mg/5 ml

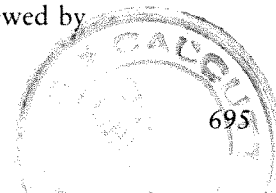
Sleep Disturbance in Posttraumatic Stress Disorder: Pathogenetic or Epiphenomenal?

In "Sleep Disturbance as the Hallmark of Posttraumatic Stress Disorder" in this issue of the *Journal*, Ross and colleagues present a provocative, thoroughgoing, and critical review of the extensive literature related to posttraumatic stress disorder (PTSD). The authors' thesis is that the dream disturbance associated with PTSD may be relatively specific for this disorder and, hence, that PTSD may be fundamentally a disorder of REM sleep mechanisms.

This thesis can be placed within the venerable theoretical framework that has posited an affective information-processing function of REM sleep. Specifically, the concept that REM sleep and dreaming are involved with, and perhaps necessary for, emotional problem solving has been suggested by Breger (1), Greenberg and Pearlman (2), and, most recently, by Cartwright (3). Common to such experiences as combat, bereavement, divorce, and other major stresses is the need for enormous cognitive-affective reorganization and reshaping. In this psychological model of REM sleep, Cartwright has suggested that REM sleep disturbance after mood-disturbing events is "an indication of a difficulty in handling waking dysphoric states, particularly in those with traits that preclude easy adaptation to the precipitating event" (3). The model would therefore predict that the severity of dysphoria after mood-disturbing events (e.g., divorce, bereavement, combat) will correlate significantly with REM sleep alterations. As predicted, in the only controlled study of REM sleep after a major mood-disturbing event, Cartwright (3) reported that in women undergoing divorce, more depressed subjects had shortened REM sleep latencies (i.e., time from sleep onset to REM onset) and irregular REM sequence—both findings similar to those noted in endogenous depression (3). At 1- to 2-year follow-up, the REM latencies of those initially most depressed remained at a lower than normal level, a finding suggestive of trait-like vulnerability to future depressions.

Viewed in this context, the claim of Ross and colleagues (that the dream disturbance of PTSD may be relatively specific) becomes controversial, but this is not to deny the *heuristic* value of the authors' speculation that PTSD may be fundamentally a disorder of REM sleep mechanisms. Similar suggestions have also been made with respect to endogenous depression, specifically, that enhanced REM sleep "pressure" plays a role in the pathogenesis of depression (4, 5). Restated somewhat, this viewpoint argues that suppression of REM sleep by antidepressant medication is the most reliable finding to correlate with favorable clinical response and, indeed, that "relief" from REM pressure is the neurobiological basis (*sine qua non*) of antidepressant efficacy (5). Taking the argument one step further, it is not yet known whether psychological interventions with proven antidepressant efficacy (e.g., cognitive behavioral therapy, interpersonal psychotherapy) also produce a normalization of REM sleep cyclicity and density concurrent with their healing effects. However, *if* REM sleep and dreaming are fundamentally involved in emotional and cognitive reshaping, and *if* abnormalities in REM sleep cyclicity and density therefore represent a breakdown in the patient's ability to adapt, *then* recovery from depression, bereavement, or PTSD alike (however mediated) should be accompanied by normalization of REM indicators. The question then becomes whether such normalization of REM sleep means that the intervention (psychological or pharmacological) has also had a protective (or prophylactic) effect.

The empirical evidence for Ross and colleagues' hypothesis (*viz.*, that the fundamental structure of REM sleep behavior is disordered in PTSD) will be viewed by



some as not very compelling, but rather as indirect and circumstantial at best. What type of empirical evidence would be necessary to support the view that dysfunctional REM sleep mechanisms are involved in the pathogenesis of PTSD? What is needed is more direct, quantitative information on the extent of overlap (and hence, specificity) between severe, recurrent anxiety dreams and rigorously defined PTSD. In addition, to my knowledge, we have little or no direct electroclinical evidence that anxiety dreams in PTSD are REM-sleep rather than non-REM sleep phenomena; and we have no evidence from controlled studies showing a reliable difference between REM-sleep and non-REM sleep mentation in PTSD. The apparent absence of consistent, solid, empirical support for abnormal REM sleep findings in PTSD (in contrast to depression) may be due partly to the failure to control for duration of PTSD and for the presence of concurrent depression, anxiety, and drug use. All of these factors represent important sources of variance ("noise") in psychiatric sleep research. Furthermore, apart from their clinical value, we need controlled studies of the pharmacotherapy and psychotherapy of PTSD-related sleep disturbance, particularly if we are to make reliable inferences about the putative role of disordered REM sleep behavior in the pathogenesis of PTSD. To my knowledge, such studies have not been published.

Finally, we are left with the uncertainty as to whether sleep disturbance in PTSD is close to the pathogenesis of this disorder (as Ross and associates suggest) or is merely epiphenomenal. (If the former, how and why does the patient's response—intense, repetitive dream experience—become the core process of the disorder?) I prefer to think that Ross and colleagues are right on this issue, because if they are not, the whole enterprise becomes scientifically uninteresting. To dissect this issue, we will need experimental paradigms that use naturalistic and pharmacologic probes to reveal the response capacity and regulatory integrity of the sleep system in PTSD. Why not simply transfer paradigms with proven utility in depression sleep research to PTSD? For example, probes such as sleep deprivation (6), REM sleep deprivation (5), and arecoline (7) have generated much information about the interrelatedness of sleep and mood regulation in depression. Similarly, might not the use of a cholinergic probe, such as arecoline, allow Ross and associates to test directly their hypothesis that PTSD involves "a problem in the timely recruitment of the entire ensemble of CNS processes which define REM sleep"? Lactate infusions during sleep might be an informative way of exploring the homology of PTSD and panic disorders.

On balance, Ross and colleagues have written an engaging and scholarly paper that cites both negative and positive evidence. Their contribution also attests, in my opinion, to the enduring intellectual vigor of psychiatric sleep research.

REFERENCES

1. Breger L: Function of dreams. *J Abnorm Psychol* 1967; 72:1-28
2. Greenberg R, Pearlman C: REM sleep and the analytic process: a psychophysiologic bridge. *Psychoanal Q* 1975; 44:392-402
3. Cartwright RD: Rapid eye movement sleep characteristics during and after mood-disturbing events. *Arch Gen Psychiatry* 1983; 40:197-201
4. Reynolds CF, Kupfer DJ: Sleep research in affective illness: state of the art circa 1987. *Sleep* 1987; 10:195-215
5. Vogel G, Vogel F, McAbee R, et al: Improvement of depression by REM sleep deprivation. *Arch Gen Psychiatry* 1980; 37:247-253
6. Reynolds CF, Kupfer DJ, Hoch CC, et al: Sleep deprivation as a probe in the elderly. *Arch Gen Psychiatry* 1987; 44:982-990
7. Sitaram N, Nurnberger J, Gershon E: Faster cholinergic REM sleep induction in euthymic patients with primary affective illness. *Science* 1980; 208:200-202

CHARLES F. REYNOLDS III, M.D.

Dr. Reynolds is Associate Professor of Psychiatry and Neurology and Director, Sleep Evaluation Center, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine. Address reprint requests to Dr. Reynolds, Sleep Evaluation Center, Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213.

Sleep Disturbance as the Hallmark of Posttraumatic Stress Disorder

Richard J. Ross, M.D., Ph.D., William A. Ball, M.D., Ph.D.,
Kenneth A. Sullivan, Ph.D., and Stanley N. Caroff, M.D.

The reexperiencing of a traumatic event in the form of repetitive dreams, memories, or flashbacks is one of the cardinal manifestations of posttraumatic stress disorder (PTSD). The dream disturbance associated with PTSD may be relatively specific for this disorder, and dysfunctional REM sleep mechanisms may be involved in the pathogenesis of the posttraumatic anxiety dream. Furthermore, the results of neurophysiological studies in animals suggest that CNS processes generating REM sleep may participate in the control of the classical startle response, which may be akin to the startle behavior commonly described in PTSD patients. Speculating that PTSD may be fundamentally a disorder of REM sleep mechanisms, the authors suggest several strategies for future research.

(Am J Psychiatry 1989; 146:697-707)

As described in DSM-III-R, posttraumatic stress disorder (PTSD) is characterized by the reexperiencing of a traumatic event in the form of repetitive dreams, recurrent, intrusive daytime recollections, and dissociative flashback episodes. In addition to a numbing of responsiveness to the outside world and various cognitive and dysphoric symptoms, evidence of excessive arousal, including exaggerated startle responses, completes the array of clinical diagnostic criteria. While symptoms of depression, anxiety, and irritabil-

ity, along with violent behavior and substance abuse, are generally viewed as secondary or associated features, it has been suggested that the cardinal manifestation of PTSD is the reexperiencing of the trauma in any or all of the aforementioned forms (1). Brett and Ostroff (2) have argued that the repetition of traumatic imagery, in the form of dreams, pseudohallucinations, or flashback episodes, forms one of the two crucial components of PTSD symptoms, the other being defensive responses to the tendency to reenact the trauma.

The sleep disturbance associated with PTSD, including most prominently the recurrent dream, remains poorly understood. In this article, we review what is known about sleep in PTSD, with the purpose of exploring clues to an underlying pathophysiology of the disordered sleep behavior in particular and other components of the PTSD symptom complex as well. We speculate on the CNS mechanisms that might be implicated in the pathogenesis and control of PTSD, arguing specifically that the phenomenology of the disorder suggests a relationship to the state of REM sleep. Hence, PTSD might involve either an inappropriate recruitment of essentially normal REM sleep processes or a coming into play of inherently dysfunctional REM sleep mechanisms. We generally limit our discussion to those cases of PTSD associated with combat experience, recognizing that forms of the illness which follow other types of trauma, such as natural disasters, rape, torture, or prisoner of war or concentration camp experiences, may share essential features.

We begin by briefly summarizing aspects of normal sleep physiology that will be discussed further in this paper. We then review the evidence that the symptom of repetitive, stereotyped anxiety dreams is relatively specific for PTSD and proceed to explain the many considerations that would appear to link the posttraumatic anxiety dream to the REM sleep state. Finally,

Received Sept. 15, 1987; revision received June 24, 1988; accepted Nov. 3, 1988. From the Philadelphia VA Medical Center and Department of Psychiatry, University of Pennsylvania, Philadelphia. Address reprint requests to Dr. Ross, Psychiatry Service (116A), Philadelphia VA Medical Center, University and Woodland Avenues, Philadelphia, PA 19104.

Supported by the VA Medical Research Service.

The authors acknowledge the scientific contributions of David F. Dinges, Ph.D., and Adrian R. Morrison, D.V.M., Ph.D.

we present the argument that the heightened startle response and the flashback experience so commonly described in PTSD may be mediated by the same neural systems that control certain components of REM sleep and that, consequently, some dysregulation of REM sleep might be implicated in the waking as well as the sleeping symptoms of PTSD.

BRIEF OVERVIEW OF NORMAL SLEEP

It has long been known that a distinct progression of stages characterizes normal sleep in the healthy adult. Each of these sleep stages (stages 1 through 4 and REM sleep) may be defined by an ensemble of physiological variables, including EEG, electromyographic, and electro-oculographic activity (3). For the purposes of this review, sleep may be divided into its REM and non-REM phases.

Tonic components, including a desynchronized EEG resembling that of waking and an atonia of the axial musculature, along with intermittent phasic events, such as conjugate REMs and twitches of distal muscles, define REM sleep. In general, sleep progresses from drowsiness through non-REM sleep to the first REM sleep episode of the night after a latency (REM latency) of 70–110 minutes. Cycling between REM sleep and non-REM sleep then continues, with the “pressure” to enter into and remain in REM sleep increasing throughout the sleep period (4). The percentage of time asleep that is occupied by REM sleep, referred to as the REM sleep percentage, typically ranges from 20% to 25% (4). The REM sleep phasic event that is best measured in clinical studies is the REM (5); REMs may be quantified (REM activity) and the ratio of REM activity to time spent in REM sleep computed (REM density).

There exists substantial evidence that the neural circuitry controlling REM sleep behavior includes pontine nuclear structures (6). One traditional hypothesis of REM sleep generation asserts that cholinergic brainstem tegmental neurons trigger REM sleep, while noradrenergic and serotonergic brainstem neurons exert an inhibitory influence (7). The REM sleep suppressant effect of many antidepressant drugs, which presumably enhance monoamine availability, has been explained on this basis (8).

The REM sleep/non-REM sleep dichotomy has been useful in investigations of the mentation accompanying sleep. It appears that dreams arising from these different sleep stages have manifestly dissimilar qualities. As regards the specific entity of distressing dreams, Hartmann (9) has defined the true nightmare as a long, frightening dream that awakens one during REM sleep. We shall adhere to this definition, except insofar as certain authors, whose findings are excerpted, may have used the term “nightmare” less categorically. A second form of anxious arousal from sleep is the night terror, distinguishable from the nightmare on the basis of its genesis during non-REM sleep,

its prominent autonomic accompaniments, and its tendency to be poorly recalled (10, 11). We shall refer to any distressing dream with unspecified physiological correlates as an anxiety dream.

IS THE ANXIETY DREAM RELATIVELY SPECIFIC FOR PTSD?

Nightmares and Other Anxiety Dreams in Normal Subjects

Before addressing the question of the relative frequency of nightmares and other types of anxiety dreams in different mental disorders, it is appropriate to review what is known about their occurrence in the normal adult population. At the outset those cautions which Hartmann (9) has advised in interpreting such prevalence data bear emphasis. Specifically, if the nightmare is defined as a long, frightening dream that awakens one during REM sleep, statistics derived from dream recall studies, and purporting to measure nightmare frequency per se, risk contamination by the anxiety dream other than the nightmare and by the night terror. Here is an instance in which even the methodology of the sleep laboratory may not provide any resolution, since it is appreciated that, in this experimental environment, subjects who otherwise experience nightmares rarely report them at all (9). Nonetheless, two studies carried out with healthy students suggest the limits of apparent nightmare frequency in the normal young adult population, essentially agreeing that 20%–24% of such subjects had nightmares at a frequency less than one per year (12, 13). While Belicky and Belicky (12) found that approximately 11% of their subjects had one or more nightmares per month, the comparable statistic reported by Feldman and Hersen was 29% (13). These figures must be compared with those derived from groups of patients with PTSD, where substantial agreement exists on an overall higher frequency of reporting of anxiety dreams.

Nightmares and Other Anxiety Dreams in PTSD

The presence of anxiety dreams, as well as other forms of sleep disturbance, in Vietnam combat veterans has been well documented (14–16). DeFazio et al. (15) reported frequent nightmares in 68% of recent Vietnam combat veterans, and van der Kolk et al. (17) found that 59% of Vietnam combat veterans had one or more nightmares per month. It is unclear how many of the combat veterans in these two studies actually met *DSM-III-R* criteria for PTSD, so it might be predicted that percentages obtained from strictly defined patient populations would be even higher.

Anxiety dreams have been described as prevalent among veterans of earlier wars as well as the Vietnam conflict (18). Furthermore, Horowitz et al. (19) investigated the signs and symptoms of PTSD in a hetero-

geneous population that had experienced any of a variety of stressors, evidently not including combat, and found that 54% of the subjects showed evidence of "bad dreams" during the week preceding the interview.

Allowing for disparities in dream collection technique and demographic differences among experimental groups, both of which might be confounding variables, there seems little doubt that anxiety dreams are reported more frequently by populations of combat veterans including patients with PTSD than by individuals with no psychiatric disorder. That they actually occur more frequently in the former group can only be inferred, especially as differences in recall ability might equally well explain the results. We suggest, however, that the nightmare should be highly accessible to recall, since by most definitions it is followed by an awakening from sleep, and its imagery likely has importance for the individual. This assertion follows from the work of Goodenough (20) and others, who have argued that immediacy of waking and salience are two of the factors that most enhance the likelihood of dream recall. It therefore seems reasonable to suppose that differences in the reporting of nightmares among various groups likely reflect differences in the rate of their occurrence rather than the frequency of their recollection. Consistent with this view is Cohen's conclusion (21), on the basis of a number of studies, that questionnaire and diary measures of dream recall frequency correlate well with those obtained in the sleep laboratory.

Nightmares and Other Anxiety Dreams in Major Depression and Schizophrenia

The question then arises, how specific is the association between the anxiety dream and PTSD? Most studies that address the issue of dreaming in relation to psychopathology suffer from serious methodological shortcomings. Criteria for patient selection and diagnosis assignment frequently remain unclear; whether psychotropic drug administration and concurrent medical illness form exclusion criteria may not be specified; and demographic characteristics of patient samples may be inadequately described (22). Relevant studies also emanate from the era preceding the *DSM-III* classification system, making particularly difficult any meaningful comparisons between other major psychiatric disorders and PTSD. Furthermore, rarely does a description of the manner of dream assessment allow the retrospective identification of samples of sleep mentation as probable nightmares.

Nightmares may be driven by a process that builds incrementally as a REM sleep episode continues (23). It follows that the abnormalities of REM sleep distribution that have been reported in depression, i.e., a reduced REM latency and a possible increase in REM sleep time during the first part of the night, might predict a heightened prevalence of nightmares in this disorder (4, 24). Furthermore, given that the phasic

events of REM sleep, including REMs, may best correlate with dream mentation, the increased REM density seen in depression might manifest itself as nightmares in some depressed patients (25). Surprisingly, actual studies of dream prevalence and content in depression provide little support for the aforesaid predictions. Depressed patients apparently dream with a normal frequency and have shortened dreams with little manifest depressive but much masochistic content (22). Reports of family members appearing in dreams seem to occur more frequently, and, after a suicide attempt, dreams may contain more morbid and violent themes (22).

With regard to schizophrenia, it is more difficult even to predict what the prevalence of actual nightmares might be. This relates to the absence of any consensus on overall sleep architecture, including that of REM sleep, in this disorder (26–28). While Hartmann's theory of the pathogenesis of nightmares in individuals with "thin boundaries" would predict a high rate of nightmares in schizophrenia, dreams of schizophrenic individuals are generally said to be bland, with relative paucity of content (9, 29, 30). Others have argued that schizophrenic patients have more primitive dreams, with more hostile and destructive content, and greater bizarreness and implausibility (22). Van der Kolk and Goldberg (31) observed one or more nightmares per month in most chronic schizophrenic patients. Interestingly, Starker and Jolin (16) found that schizophrenic individuals who had been in combat had more nightmares than those who had not. Thus, while preliminary data are consistent with a prominent place for the nightmare in the symptoms of schizophrenia, contradictory findings exist. We recognize that schizophrenia might eventually prove an exception to our assertion that the nightmare most specifically characterizes PTSD. In that case, however, pathophysiological mechanisms common to both disorders might ultimately be revealed.

Nightmares in Dream Anxiety Disorder

DSM-III-R includes a parasomnia referred to as dream anxiety (or nightmare) disorder. Given that the essential diagnostic criterion is "repeated awakenings from sleep with detailed recall of frightening dreams," this is another disorder that, by definition, involves the reexperiencing of anxiety dreams. In a departure from its usual nonmechanistic orientation, *DSM-III-R* attributes the dream anxiety episodes in dream anxiety disorder to periods of REM sleep. While it is noted that a major stressful life event appears to antedate dream anxiety disorder in a majority of cases, PTSD is not specifically mentioned as a differential diagnostic consideration. Thus, the nature of any relationship between PTSD and dream anxiety disorder remains to be determined. It seems possible that clarification of the complex nosological issues will provide additional support for a REM sleep mechanism underlying the posttraumatic anxiety dream.

DO REM SLEEP MECHANISMS UNDERLIE THE ANXIETY DREAM DESCRIBED IN PTSD?

PTSD Dreams: True Nightmares?

While it has long been recognized that dreaming may occur during non-REM sleep as well as REM sleep, certain features appear to distinguish these two forms of sleep mentation (25, 32). In particular, there is substantial agreement that the recall occurring out of REM sleep contains more vivid, bizarre, and frankly dreamy content than that associated with non-REM sleep. Other descriptors of REM sleep dream reports, in comparison to non-REM sleep reports, include "more highly elaborated," "[showing] . . . less correspondence to the waking life of the subject," better recalled, less thought-like, less conceptual, less plausible, more visual, more emotional, and less pleasant (25). In terms of the sheer abundance of mentation, there appears to be a higher likelihood of dream recall when subjects are awakened from REM sleep than from non-REM sleep (25, 33). Reviewing the subject of mental activity during sleep, Rechtschaffen (25) has concluded: "The net result is that REM and NREM are highly discriminable on the basis of the amount and quality of mental activity that they yield." Indeed, one early study found a high degree of resolution between REM sleep and non-REM sleep dream reports when judges had access to information about the quantity and quality of mentation elicited during a series of awakenings (34).

The phenomenology of the dream disturbance in PTSD can now be viewed in the context of these acknowledged differences between REM sleep and non-REM sleep mentation. Veterans with PTSD generally report awakening from a dream that involves reliving the trauma, experiencing strong emotions that would have been appropriate reactions to the original traumatic event—usually rage, intense fear, or grief. Less often, they describe awakening in terror without recalling any of the actual dream (35). The content of PTSD dreams may vary widely (36). It may consist of rather apparent transformations of battle scenes (37, 38). Alternatively, it may have elements of death, dying, or threat to self that are accompanied by anxiety, fear, or other emotions that approximate the feeling state at the time of the trauma (39). Most frequently, however, posttraumatic dreams depict the actual traumatic event, and they are often repetitive replicas of true combat scenes, appearing more like a memory than a dream or a fantasy and tending to be replayed over and over again (9, 40). There is some evidence that veterans with definite and severe PTSD are those whose dreams most closely resemble exact memories (9).

These descriptions of the typical dream mentation in PTSD lead to the view that the posttraumatic anxiety dream is more likely a manifestation of REM sleep than non-REM sleep and hence represents an actual nightmare. Although the dreams associated with PTSD

can assume a variety of forms, they are well characterized as vivid, affect-laden, disturbing, and outside the realm of current waking experience (although replicative of an earlier life experience). All of these are qualities of dreams presumably arising from REM sleep. In addition, posttraumatic anxiety dreams are generally easy to recall, a point that traditionally has been used to distinguish REM sleep from non-REM sleep dreams. The hypothesis linking dysfunctional REM sleep mechanisms to the pathophysiology of PTSD rests on these crucial logical assumptions.

One important caveat to this argument pertains to the classical observation that a specific form of anxious arousal, in some ways resembling the posttraumatic dream, may also occur out of non-REM sleep (10, 11). The so-called night terror or incubus typically occurs early in sleep and is associated with marked elevations in heart and respiratory rates. The subject is most often confused and disoriented, displays perseverative movements, and is generally reported to manifest no memory for the event. However, in investigations of the ability to recall any mental content, rates as high as 50% have been cited (41). Whether the described ideation represents non-REM sleep dreaming or a phenomenon of postarousal confusion remains to be determined. Night terrors are felt to occur very rarely in the adult population. While their etiology remains obscure, the possibility of their causation, at least in part, by traumatic stress has been considered (42).

There are at least two reasons to suppose that neurophysiological events responsible for the night terror might participate in the anxiety dream of PTSD. First, the posttraumatic anxiety dream, like the night terror, frequently occurs early in the night (40). Second, it is often accompanied by gross body movements (40). The second presents possibly the greater argument in favor of a non-REM sleep mechanism underlying the posttraumatic dream, since REM sleep has traditionally been characterized by generalized muscle atonia, in concert with an activated EEG and phasic REMs.

However, an important recent advance in sleep research has involved the recognition of a potentially new class of parasomnia, that in which an overt behavioral disturbance occurs during REM sleep (43–46). Schenck et al. (43) reported on five elderly patients, all exhibiting aggressive or even injurious behavior during sleep and all manifesting significant REM sleep abnormalities on polysomnography. Specifically, the usual atonia of the chin musculature was only variably present, limb twitching was accentuated, and movements, some potentially harmful, were observed on videotape. While most of the subjects had demonstrable neurological disorders, one was considered to have an idiopathic REM sleep disturbance. In a larger series of patients with "REM sleep behavior disorder," 60% had no evident neurological etiology (47). Consequently, the occurrence of movement during an anxiety dream, as may be seen in PTSD, need not eliminate the possibility of a REM sleep mechanism. The posttraumatic sleep disturbance may well

belong to a group of parasomnias associated with REM sleep.

Polysomnographic Studies of PTSD: Evidence for REM Sleep Abnormalities

Despite the widespread recognition of PTSD since the Vietnam war and the frequency with which combat veterans present with sleep-related complaints, relatively few studies have employed objective measures of sleep in PTSD patients. It should be recognized at the outset that sleep laboratory studies of any clinical condition may be subject to the criticism that the results are contaminated by the unnaturalistic experimental environment. Even the inclusion of a control group in the experimental design hardly counters the objection that patients with an anxiety disorder, particularly one characterized by withdrawal from social interactions and exaggerated reactivity to unexpected sensory stimuli, might respond differently to the laboratory setting. The nearly standard use of one adaptational night, before the actual collection of data for analysis, may offer the best approach to minimizing this source of error. Attempts to use polysomnographic techniques to investigate the sleep disturbance of PTSD are further complicated by the oft-repeated observation that nightmares are infrequently reported in the sleep laboratory, even among subjects who otherwise complain of nightmares (9). This may be taken as one additional piece of evidence that some aspects of sleep behavior are substantially altered in the laboratory environment.

With the exception of one recent investigation of elderly subjects with PTSD, which found no REM sleep abnormality (48), the results of polysomnographic studies of PTSD generally fall into two categories, one consistent with a heightened tendency to enter REM sleep and the other emphasizing a diminished "pressure" toward REM sleep. The investigation by Greenberg et al. (49) represents the former. Vietnam combat veterans with a diagnosis of "war neurosis," based on the presence of recurring nightmares, prominent startle reactions, and dysphoria, showed a high prevalence of nights with shortened REM latency. In addition, each patient's psychological state was assessed with 5-minute verbal samples rated in terms of "defensive strain," and there was a statistically significant inverse correlation between defensive strain score and REM latency. A high REM density was also noted. The authors inferred that the psychodynamic status of a patient influenced the pressure to dream, as measured polysomnographically, and they hypothesized that REM sleep is involved in the processing and integrating of stressful experiences. The absence of a control population, no systematic inclusion of an adaptational night in the sleep laboratory, and the failure to awaken subjects out of non-REM sleep as well as REM sleep limit the conclusions that can be drawn regarding the specificity of the findings for PTSD and the nature of the relationship between the posttraumatic anxiety dream and REM sleep, as opposed to non-REM sleep.

Kauffman et al. (50) also found a decreased REM latency in PTSD patients, but most subjects were alcohol abusers who had been free of alcohol for an unspecified period of time, raising the possibility of alcohol withdrawal as a confounding variable. Further support for the possibility of heightened REM pressure in the aftermath of trauma derives from a study of the sleep of women undergoing divorce (51). Those subjects presumed to be in the greatest distress over the dissolution of their marriages showed the shortest REM latencies and highest REM densities. There have also been demonstrations that exposure to even a mildly stressful experience before sleep is reflected acutely in increased REM density and increased REM sleep awakenings (52). In this context, the anxiety dreams and insomnia associated with PTSD may be seen as reflections of a repetitive, unsuccessful attempt to reconstitute psychological defenses.

Unfortunately, quite the opposite conclusion may be drawn from the work of Schlosberg and Benjamin (53), who reported polysomnographic data from patients with acute "combat fatigue." Pervasive abnormalities of sleep were observed. Of particular importance, REM latency was increased and REM sleep periods were rare and short. Thus, the pressure to enter REM sleep was felt to be diminished in the aftermath of trauma, at least acutely. Lavie et al. (54), in a controlled study of patients with "combat neurosis," also found an increased REM latency and evidence for a diminished average REM sleep episode duration and reduced REM sleep percentage as long as 2 to 2½ years after the original war-related trauma. The only patients to report war-related nightmares during the study showed mid-sleep awakenings clustered around expected or actual REM sleep periods, suggesting to the authors that these patients suffered from "dream-interruption insomnia." This cluster of REM sleep abnormalities was thought to reflect an avoidance of REM sleep and a forestalling of highly emotional dreams, an interpretation diametrically contrary to that of Greenberg et al. (49).

Van der Kolk et al. (40) compared PTSD patients to noncombat veterans with lifelong nightmares. The nightmares of PTSD patients occurred earlier in the sleep cycle. There was evidence that sleep mentation in PTSD is not confined to REM sleep periods and in fact may arise out of various stages of sleep, including stage 2. Schlosberg and Benjamin (53) had also reported stage 2-associated dreams in their patients with acute combat fatigue. On the basis of a single case study, Hartmann (9) concurred in assigning the posttraumatic nightmare to both the REM sleep and non-REM sleep states. Both Hartmann (9) and Kramer et al. (55) have suggested that in PTSD patients, common themes may arise out of REM sleep and non-REM sleep.

In summary, for reasons having to do with small patient populations studied at different phases of the illness and uncontrolled and otherwise problematic experimental designs, no conclusive statements can be made regarding the actual sleep polysomnographic

correlates of PTSD. Certainly there is substantial evidence for disordered REM sleep function. Negative results from one study in an elderly population may only suggest that age and duration of PTSD symptoms be considered crucial factors affecting sleep EEG measures. As we have seen, no consensus exists as to whether there is a heightened or reduced tendency to enter into and remain in REM sleep and what psychodynamic significance either possibility might hold. Alternatively, the REM sleep abnormality might be manifest as an altered density of phasic events, perhaps without any change in the broad outlines of REM sleep distribution at all. Abnormal non-REM sleep mechanisms, particularly those underlying stage 2 sleep, may also be involved in the generation of PTSD symptoms.

Pharmacotherapy of the Sleep Disturbance of PTSD: Insights Into a REM Sleep Mechanism

Many psychotropic agents have prominent effects on REM sleep. It is important, then, to question whether data derived from pharmacological treatment studies provide support for the hypothesis that REM sleep systems are dysfunctional in PTSD. To date, no double-blind, placebo-controlled studies have been reported, and the rationales for open clinical trials have generally focused on elements of the PTSD symptom complex other than the sleep difficulties (56). Yet some insights into the drug treatment of the sleep disturbance of PTSD have been provided.

The results of several studies suggest a therapeutic role for the monoamine oxidase inhibitors (MAOIs) in PTSD (57–59). In a preliminary, uncontrolled, and nonblind investigation, Hogben and Cornfield (57) reported a dramatic response to phenelzine in five inpatients with PTSD who had not previously responded to an antipsychotic drug, a tricyclic antidepressant, and psychotherapy. While inclusion criteria were not stated, all patients had nightmares, as well as flashbacks and frequent panic attacks. Within days after treatment started, nightmares abated, as did flashbacks, startle responses, panic, and generalized anxiety. Milanese et al. (58) also speculated that PTSD patients with nightmares, hyperalertness, irritability, and anxiety might benefit from phenelzine treatment. In contrast, van der Kolk (60) observed that an increased vividness of daytime traumatic memories in four of seven patients treated with phenelzine limited the value of this agent in conditions characterized by explosive hyperreactivity to mild stimuli.

Efficacy of the tricyclic antidepressants in treating PTSD has been reported by several investigators. Van der Kolk (60) suggested that amitriptyline's beneficial effect on sleep is not its primary therapeutic mechanism. Bleich et al. (61) remarked that the generally favorable response to amitriptyline was most prominent with symptoms of sleep disturbance, as well as exaggerated startle and memory and concentration problems. Both Burstein (62) and Marshall (63) re-

ported the usefulness of imipramine in suppressing sleep difficulties in PTSD.

Positive results of lithium treatment in PTSD patients with histories of frequent nightmares, as well as explosiveness, emotional detachment, guilt, and prominent startle reactions, have been reported by van der Kolk (60). Kolb and Motalipassi (64) have proposed that the symptoms of PTSD can best be conceptualized as a "conditioned emotional response" to environmental stimuli reminiscent of the traumatic event and that this conditioned response may be related to excessive central and/or peripheral adrenergic sympathetic activation. Therefore, they conducted clinical trials of the α_2 agonist clonidine and the beta adrenergic blocker propranolol. Improvement in the sleep disturbance, as well as in the symptoms of hyperalertness, occurred in the vast majority of patients (65). When the benzodiazepines have been used to treat PTSD, any improvement in sleep has been viewed as secondary to an amelioration of motor and autonomic hyperreactivity (66). Maintenance antipsychotic treatment has not been recommended for the treatment of PTSD, and any effects of such a regimen on the sleep disturbance per se have not been documented.

It may be significant that the MAOI phenelzine, which arguably has the best documented efficacy in the treatment of PTSD sleep problems, is otherwise known to reduce REM sleep profoundly and protractedly (67). Furthermore, with at least four separate reports of the value of some tricyclic antidepressants in controlling the sleep disturbance of PTSD, the known REM sleep suppressant effect of these drugs assumes considerable importance. While there is little doubt that the acute administration of a range of tricyclic antidepressants decreases REM sleep percentage (68), some uncertainty exists regarding long-term effects, specifically the degree of tolerance that develops after repeated drug administration (68). However, the available data would suggest that residual REM sleep suppression is sufficient to be consistent with the view that a reduction in REM sleep is a therapeutic mechanism in PTSD. Additional support for this corollary of a REM sleep hypothesis of PTSD generation comes from the fact that lithium carbonate and clonidine, which may also improve the sleep disorder of PTSD, both significantly decrease REM sleep (69–71). While the beta blockers have less clear-cut effects on REM sleep propensity, their clinical utility in PTSD is also not established (71). The same may be said of the benzodiazepines and the antipsychotic drugs.

ARE BEHAVIORAL MANIFESTATIONS OF PTSD OTHER THAN THE ANXIETY DREAM ALSO CONSEQUENCES OF DISORDERED REM SLEEP MECHANISMS?

A hypothesis concerning the pathophysiology of a multifaceted disorder has particular heuristic merit if, having developed from ideas about one specific symp-

tom, it can then give rise to explanations of others. The invoking of REM sleep mechanisms to explain the phenomenology of PTSD emerges most apparently from the observation of prominent anxiety dreams in PTSD patients. We also hypothesize that dysfunctional REM sleep circuitry might participate in the exaggerated startle response described in PTSD. This suggestion follows directly from what is known of the neurophysiology of REM sleep.

REM sleep shows marked similarities to the waking state. It is characterized by a desynchronized EEG similar to that of waking and hippocampal regular slow waves, known as theta activity, resembling those recorded during activated waking. In addition, pontogeniculo-occipital (PGO) spikes, so-named because they were first detected in the pons, lateral geniculate body, and visual cortex of animals, are a phasic manifestation of REM sleep apparently analogous to eye movement potentials observed during orienting responses of wakefulness (72, 73). Important support for the notion of comparable patterns of CNS activity during REM sleep and waking is provided by the phenomenon of REM sleep without atonia, which has been created in cats by making bilateral lesions of the dorsolateral pontine tegmentum. Animals so treated remarkably cycle in and out of a state that resembles normal REM sleep except that they retain significant muscle tone (74). Thus, while normal animals display generalized atonia during REM sleep, animals with these lesions are in fact able to demonstrate a variety of behaviors. In this way, REM sleep without atonia has been likened to a "window on the sleeping brain" (74). The fact that the behaviors that have been observed resemble those associated with orienting, searching, startle, or even aggressive displays has been taken as evidence that REM sleep is a state of continuous alerting (74).

Other experiments in animals provide at least two reasons for supposing that the phasic events of REM sleep, in particular, are related to startle behavior. First, electromyographic patterns recorded during these phasic events resemble those recorded during the startle response, and second, "startling" environmental stimuli can elicit PGO spikes during sleep (75, 76). Two problems with this analysis are that 1) the startle reflex has best been investigated in the rat, while phasic events have generally been studied in the cat, and 2) the brainstem anatomic loci controlling these two behaviors appear to be different (6, 77). Neither provides a compelling caveat, however, especially as additional cross-species studies may prove consistent, and the aforesaid disparate brainstem centers may yet be found to operate in series (75). While generalizing from these findings in animals to possibly analogous clinical phenomena risks interpretive errors, we hypothesize that neural circuitry involved in the sleep and dream disturbance of PTSD may also be implicated in the accentuated startle behavior. The hypothesis linking PTSD to REM sleep mechanisms gains additional strength

from its capacity to explain the heightened startle as well as the posttraumatic anxiety dream.

As noted earlier, *DSM-III-R* criteria for diagnosing PTSD recognize that the trauma may be reexperienced as a "sudden acting or feeling as if the traumatic event were recurring," as well as in the form of a dream or waking memory. While the possibility of some physiological homology between the dream disturbance and the so-called flashback has been raised, specific commonalities have not been proposed (78, 79). On the basis of several reports in the literature that the propensity to enter REM sleep normally varies in a circadian fashion, with a greater likelihood during the rising portion of the body temperature cycle and persisting into the morning, it might be proposed that the daytime flashback reflects a balance of forces propelling the CNS into a REM sleep organizational state (80–83). In another context, Fiss has made explicit the view that mentation characteristic of REM sleep can be displayed during wakefulness (84).

FUTURE RESEARCH DIRECTIONS AND CONCLUSIONS

The possibility that CNS mechanisms fundamental to REM sleep generation are involved in the pathophysiology of PTSD suggests several directions for future research efforts. First, a precise description of the actual sleep patterns of a large cohort of PTSD patients is essential. As we have seen, independent data suggest that dreams that arise out of REM sleep, as compared to non-REM sleep, can be distinguished by a blind observer (34). There also exists a consensus that typical REM sleep nightmares show striking differences from non-REM sleep night terrors (9, 42). Hence, patients' self-reports about the timing, content, and quality of their nighttime anxiety dreams might further implicate REM sleep systems in the genesis of PTSD symptoms. It may also be crucial to elicit information from subjects' bed partners, given the tendency of PTSD patients to display an alexithymic-like incapacity to relate significant emotional material (85). Because it is generally accepted that the rate of dream recall occurring out of non-REM sleep is lower than that associated with REM sleep, as well as more highly influenced by sources of variance deriving from dream collection technique, data obtained from questionnaire and sleep diary studies may well be biased toward the relative underreporting of non-REM sleep mentation (33). The intrusive reexperiencing of the traumatic event may actually be manifest in non-REM sleep as well as REM sleep but perhaps more difficult to identify (9).

Polysomnographic studies should provide even more definitive data by which to judge the adequacy of a REM sleep hypothesis of PTSD pathogenesis. The identification of appropriate groups of index and control subjects may be complicated by the reportedly frequent concurrence of major depressive illness and var-

ious forms of substance abuse with PTSD (1). Because depression and drug withdrawal almost certainly have their own specific polysomnographic patterns, which need to be distinguished from those of PTSD, rigorous criteria for the selection of patient and control populations will be crucial.

While it must be expected that nightmare phenomena will rarely be reported in a sleep laboratory setting, measures of REM sleep episode frequency and duration, REM sleep percentage, REM latency, and REM density should be easily obtainable and should yield important insights into tonic and phasic REM sleep components in PTSD patients. According to Hartmann's concept (23) of "D pressure," defined as the tendency for a nightmare to occur that builds proportionally with the length of a REM sleep episode, increases in REM sleep episode duration and REM sleep percentage might be expected to occur in PTSD. With analogous reasoning, a diminished REM latency could also be predicted. Alternatively, the overall topography of REM sleep might remain unaltered in PTSD, while the frequency or amplitude of REM sleep phasic events were augmented. Strong support for the latter possibility is provided by the substantial evidence, previously reviewed by Rechtschaffen (25), for some nonspecific correlation between the abundance of REMs and the content of sleep mentation in normal subjects. On the other hand, Hefez et al. (86) remarked on an unexpectedly poor correspondence between REM activity and dream recall in posttraumatic patients. We have noted how the extant polysomnographic studies of PTSD provide data consistent with several of these predictions, at the same time revealing explicit contradictions.

One important area of disagreement pertains to whether the recruitment of REM sleep mechanisms represents an effective adaptation enabling the patient to process stressful material or, alternatively, reflects the central problem in PTSD. These conflicting views appear reminiscent of the dilemma that earlier faced psychoanalytic theorists. Our work provides a more empirical approach to the study of PTSD but nonetheless represents a reemphasis on the sleep and dream disturbance postulated by Freud and others to be a key element in understanding the "traumatic neurosis."

Insomnia and recurrent, anxiety-laden dreams figured significantly in Freud's description (87) of the traumatic neurosis, and his speculations about the nature of the "traumatic dream" encouraged him to examine more closely his famous dictum that a dream represents the disguised fulfillment of a repressed wish. He stated the question succinctly: "What wishful impulse could be satisfied by harking back in this way to this exceedingly traumatic experience?" (87). He responded that the traumatic neurosis was a condition in which the dream mechanism fails, wish fulfillment does not occur, and there is no reduction in the anxiety associated with the trauma. In this view, a disturbance of the dream mechanism itself was central to the pathophysiology of the traumatic neurosis. In contrast, Fe-

nel (88) viewed the posttraumatic dream as a means of discharging the anxiety generated by overwhelmingly stressful events. Still other psychoanalytic writers described the posttraumatic dream more explicitly in terms of its defensive function (89). Thus psychoanalytic theory, as it has evolved from Freudian conceptions, reflects an ambiguity about the adaptive role of the posttraumatic dream nearly analogous to that confronted by the polysomnographic literature.

It might be argued that strategies for treating the sleep disturbance of PTSD express a similar uncertainty regarding the role of the anxiety dream and REM sleep mechanisms. On the one hand, there is the evidence that drugs with some clinical efficacy almost invariably suppress REM sleep. This observation parallels the argument that repetitive, stereotyped anxiety dreams and a tendency toward REM sleep are expressions of the essential pathophysiology of PTSD and must be controlled before symptoms can remit. One clinical implication might be that a selective REM sleep deprivation paradigm, analogous to that used by Vogel (90) in endogenous depression, ought to be applied to PTSD subjects. Seemingly contradictory data emerge from studies in which the reexposure to posttraumatic dream material has been used successfully in the treatment of PTSD. Such therapeutic methods are perhaps best exemplified by the imaginal flooding technique described by Keane and Kaloupek (91). Given the very preliminary nature of all findings that relate to treating PTSD, it is to be expected that future investigations will clarify appropriate therapeutic modalities and mechanisms and, by implication, elucidate the exact role of REM sleep systems in the generation and maintenance of PTSD symptoms.

Essential to the hypothesis invoking REM sleep systems in the pathophysiology of PTSD is the expectation that impairments of waking, as well as sleep, functions can thereby be explained. Evidence from animal studies links the startle response to REM sleep behavior. Therefore, formal testing of the properties of the startle response in PTSD patients, compared to control populations, might reveal significant differences, particularly some which covaried with REM sleep abnormalities. While two groups of investigators have already documented enhanced autonomic responsivity to emotionally meaningful auditory or audiovisual stimuli, reminiscent of combat experiences, it seems doubtful that such behavior is truly startle, as classically described (77, 92). Davis (77) has emphasized that the startle reflex is characterized by a very short latency, with the earliest signs of electromyographic activity in man occurring 14 msec after the presentation of a loud click. Furthermore, at least in the rat, the acoustic startle circuitry mediating the shortest latency muscle response includes structures no higher than the pontine level of the neuraxis. Accordingly, the autonomic hyperreactivity to affectively relevant stimuli that has been described in PTSD patients, and which presumably depends on higher limbic and cortical pathways, likely represents a secondary elaboration of

startle behavior rather than a manifestation of primary startle itself. If they are to address the question of dysfunctional REM sleep mechanisms in PTSD, future studies will need to concentrate on the properties of startle behavior, as rigorously defined by Davis and others, in this patient population.

We have suggested that the flashback experience represents the emergence into wakefulness of a form of mentation otherwise associated with REM sleep. Others have observed that the potential for entering REM sleep during a daytime nap varies with the position of the nap in the diurnal cycle and that dreaming occurs during daytime naps (80–83). The REM sleep hypothesis of PTSD would predict that flashback frequency should parallel the curve of REM sleep propensity during the morning, afternoon, and evening. Therefore, the typical circadian cycle of REM sleep first needs to be confirmed in PTSD patients by using a repeated naps paradigm (80). Whether the occurrence of flashbacks varies similarly with circadian phase can then be ascertained.

The exact nature of any REM sleep dysfunction in PTSD remains a matter for speculation. While the simplest formulations would posit a problem in the timely recruitment of the entire ensemble of CNS processes that define REM sleep, an alternative, but not necessarily exclusive, hypothesis would be that the fundamental structure of REM sleep behavior is disordered. As an example, we have raised the possibility of a disturbance in phasic event generation, as revealed by REM density measurements. In addition, the many reports of movements during dreams in PTSD patients suggest a relation to a recently described clinical parasomnia characterized by REM sleep with persisting muscle tone. That there may exist an animal model of this phenomenon, i.e., REM sleep without atonia as observed in cats with bilateral pontine tegmental lesions, enhances the likelihood that the neurophysiological and neuropharmacological mechanisms underlying PTSD might eventually be understood with great clarity (74).

REFERENCES

- Green BL, Lindy JD, Grace MC: Post-traumatic stress disorder: toward DSM-IV. *J Nerv Ment Dis* 1985; 173:406–411
- Brett EA, Ostroff R: Imagery and posttraumatic stress disorder: an overview. *Am J Psychiatry* 1985; 142:417–424
- Rechtschaffen A, Kales A: A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Los Angeles, UCLA Brain Information Service/Brain Research Institute, 1968
- Kupfer DJ, Thase ME: The use of the sleep laboratory in the diagnosis of affective disorders. *Psychiatr Clin North Am* 1983; 6:3–25
- Aserinsky E, Kleitman N: Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science* 1953; 118:273–274
- Vertes RP: Brainstem control of the events of REM sleep. *Prog Neurobiol* 1984; 22:241–288
- Hobson JA, McCarley RW, Wyzinski PW: Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. *Science* 1975; 189:55–58
- McCarley RW: REM sleep and depression: common neurobiological control mechanisms. *Am J Psychiatry* 1982; 139:565–570
- Hartmann E: *The Nightmare: The Psychology and Biology of Terrifying Dreams*. New York, Basic Books, 1984
- Broughton RJ: Sleep disorders: disorders of arousal? *Science* 1968; 159:1070–1078
- Kales JD, Kales A, Soldatos CR: Night terrors. *Arch Gen Psychiatry* 1980; 37:1413–1417
- Belicky D, Belicky K: Nightmares in a university population. *Sleep Res* 1982; 11:116
- Feldman MJ, Hersen M: Attitudes toward death in nightmare subjects. *J Abnorm Psychol* 1967; 72:421–425
- Card JJ: *Lives After Vietnam*. Lexington, Mass, DC Heath, 1983
- DeFazio VJ, Rustin S, Diamond A: Symptom development in Vietnam era veterans. *Am J Orthopsychiatry* 1975; 45:158–163
- Starker S, Jo'in A: Imagery and fantasy in Vietnam veteran psychiatric inpatients. *Imagination, Cognition and Personality* 1982; 2:15–22
- van der Kolk BA, Hartmann E, Burr A, et al: A survey of nightmare frequencies in a veterans outpatient clinic. *Sleep Res* 1980; 9:229
- Archibald HC, Long DM, Miller C, et al: Gross stress reaction in combat—a 15-year follow-up. *Am J Psychiatry* 1962; 119:317–322
- Horowitz MJ, Wilner N, Kaltreider N, et al: Signs and symptoms of posttraumatic stress disorder. *Arch Gen Psychiatry* 1980; 37:85–92
- Goodenough DR: Dream recall: history and current status of the field, in *The Mind in Sleep*. Edited by Arkin AM, Antrobus JS, Ellman S. Hillsdale, NJ, Lawrence Erlbaum Associates, 1978
- Cohen DB: Toward a theory of dream recall. *Psychol Bull* 1974; 81:138–154
- Kramer M, Roth T: Dreams in psychopathology, in *Handbook of Dreams*. Edited by Wolman BB. New York, Van Nostrand Reinhold, 1979
- Hartmann E: A note on the nightmare. *Int Psychiatry Clin* 1970; 7:192–197
- Kupfer DJ: REM latency: a psychobiological marker for primary depressive disease. *Biol Psychiatry* 1976; 11:159–174
- Rechtschaffen A: The psychophysiology of mental activity during sleep, in *The Psychophysiology of Thinking*. Edited by McGuigan FJ, Schoonover RA. New York, Academic Press, 1973
- Kupfer DJ, Wyatt RJ, Scott J, et al: Sleep disturbance in acute schizophrenic patients. *Am J Psychiatry* 1970; 126:1213–1223
- Zarcone VP Jr, Benson KL, Berger PA: Abnormal rapid eye movement latencies in schizophrenia. *Arch Gen Psychiatry* 1987; 44:45–48
- Benson KL, Zarcone VP Jr: Testing the REM sleep phasic event intrusion hypothesis of schizophrenia. *Psychiatry Res* 1985; 15:163–173
- Dement W: Dream recall and eye movements during sleep in schizophrenics and normals. *J Nerv Ment Dis* 1955; 122:263–269
- Zarcone VP Jr: Sleep and schizophrenia. *Psychiatr Annals* 1979; 9:29–40
- van der Kolk BA, Goldberg HL: Aftercare of schizophrenic patients: psychopharmacology and consistency of therapists. *Hosp Community Psychiatry* 1983; 4:340–343
- Foulkes WD: Dream reports from different stages of sleep. *J Abnorm Soc Psychol* 1962; 65:14–25
- Herman JH, Ellman SJ, Roffwarg HP: The problem of NREM dream recall re-examined, in *The Mind in Sleep*. Edited by Arkin AM, Antrobus JS, Ellman SJ. Hillsdale, NJ, Lawrence Erlbaum Associates, 1978
- Monroe LJ, Rechtschaffen A, Foulkes D, et al: Discriminability of REM and NREM reports. *J Pers Soc Psychol* 1965; 2:456–460
- Arnold AL: Diagnosis of post-traumatic stress disorder in Viet Nam veterans, in *The Trauma of War: Stress and Recovery in*

- Viet Nam Veterans. Edited by Sonnenberg SM, Blank AS Jr, Talbott JA. Washington, DC, American Psychiatric Press, 1985
36. Ziarnowski AP, Broida DC: Therapeutic implications of the nightmares of Vietnam combat veterans. *VA Practitioner* 1984; 1:63-68
37. Grinker RR, Spiegel JP: *Men Under Stress*. New York, McGraw-Hill, 1945
38. Kardiner A, Spiegel H: *War Stress and Neurotic Illness*. New York, Hoeber, 1947
39. Scurfield RM: Post-trauma stress assessment and treatment: overview and formulations, in *Trauma and Its Wake: The Study and Treatment of Post-Traumatic Stress Disorder*. Edited by Figley CR. New York, Brunner/Mazel, 1985
40. van der Kolk B, Blitz R, Burr W, et al: Nightmares and trauma: a comparison of nightmares after combat with lifelong nightmares in veterans. *Am J Psychiatry* 1984; 141:187-190
41. Kramer M: Dream disturbances. *Psychiatr Annals* 1979; 9: 366-376
42. Carlson CR, White DK: Night terrors: a clinical and empirical review. *Clin Psychol Rev* 1982; 2:455-468
43. Schenck CH, Bundlie SR, Ettinger MG, et al: Chronic behavioral disorders of human REM sleep: a new category of parasomnia. *Sleep* 1986; 9:293-308
44. Ishigooka J, Westendorp F, Oguchi T, et al: Somnambulistic behavior associated with abnormal REM sleep in an elderly woman. *Biol Psychiatry* 1985; 20:1003-1008
45. Gagnon P, DeKoninck J: Repetitive head movements during REM sleep. *Biol Psychiatry* 1985; 20:176-178
46. Oswald I, Kirstine A: Rhythmic raiding of refrigerator related to rapid eye movement sleep. *Br Med J [Clin Res]* 1986; 292:589
47. Schenck CH, Hurwitz TD, Mahowald MW: REM sleep behavior disorder (letter). *Am J Psychiatry* 1988; 145:652
48. van Kammen W, Christiansen C, van Kammen D, et al: Sleep and the POW experience. *Sleep Res* 1987; 16:291
49. Greenberg R, Pearlman CA, Gampel D: War neuroses and the adaptive function of REM sleep. *Br J Med Psychol* 1972; 45: 27-33
50. Kauffman CD, Reist C, Djenderedjian A, et al: Biological markers of affective disorders and posttraumatic stress disorder: a pilot study with desipramine. *J Clin Psychiatry* 1987; 48:366-367
51. Cartwright RD: Rapid eye movement sleep characteristics during and after mood-disturbing events. *Arch Gen Psychiatry* 1983; 40:197-201
52. Baekeland F, Koulack D, Lasky R: Effects of a stressful presleep experience on electroencephalograph-recorded sleep. *Psychophysiology* 1968; 4:436-443
53. Schlosberg A, Benjamin M: Sleep patterns in three acute combat fatigue cases. *J Clin Psychiatry* 1978; 39:546-549
54. Lavie P, Hefez A, Halperin G, et al: Long-term effects of traumatic war-related events on sleep. *Am J Psychiatry* 1979; 136: 175-178
55. Kramer M, Schoen LS, Kinney L: The dream experience in dream-disturbed Vietnam veterans, in *Post-Traumatic Stress Disorder: Psychological and Biological Sequelae*. Edited by van der Kolk BA. Washington, DC, American Psychiatric Press, 1984
56. Friedman MJ: Toward rational pharmacotherapy for posttraumatic stress disorder: an interim report. *Am J Psychiatry* 1988; 145:281-285
57. Hogben GL, Cornfield RB: Treatment of traumatic war neurosis with phenelzine. *Arch Gen Psychiatry* 1981; 38:440-445
58. Milanes FJ, Mack CN, Dennison J, et al: Phenelzine treatment of post-Vietnam stress syndrome. *VA Practitioner* 1984; 1:40-49
59. Walker JI: Chemotherapy of traumatic war stress. *Milit Med* 1982; 147:1029-1033
60. van der Kolk BA: Psychopharmacological issues in posttraumatic stress disorder. *Hosp Community Psychiatry* 1983; 34:683-691
61. Bleich A, Siegel B, Garb R, et al: Post-traumatic stress disorder following combat exposure: clinical features and psychopharmacological treatment. *Br J Psychiatry* 1986; 149:365-369
62. Burstein A: The treatment of post-traumatic stress disorder with imipramine. *Psychosomatics* 1984; 25:683-687
63. Marshall JR: The treatment of night terrors associated with the posttraumatic syndrome. *Am J Psychiatry* 1975; 132:293-295
64. Kolb LC, Mutalipassi LR: The conditioned emotional response: a subclass of the chronic and delayed post-traumatic stress disorders. *Psychiatr Annals* 1982; 12:979-987
65. Kolb LC: The post-traumatic stress disorders of combat. *Milit Med* 1984; 149:237-243
66. Malloy PE, Fairbank JA, Keane TM: Validation of a multimethod assessment of post-traumatic stress disorder in Vietnam veterans. *J Counsel Clin Psychology* 1983; 51:488-494
67. Wyatt RJ, Fram DH, Kupfer DJ, et al: Total prolonged drug-induced REM sleep suppression in anxious-depressed patients. *Arch Gen Psychiatry* 1971; 24:145-155
68. Dunleavy DLF, Brezinova V, Oswald I, et al: Changes during weeks in effects of tricyclic drugs on the human sleeping brain. *Br J Psychiatry* 1972; 120:663-672
69. Kupfer DJ, Reynolds CF III, Weiss BL, et al: Lithium carbonate and sleep in affective disorders: further consideration. *Arch Gen Psychiatry* 1974; 30:79-84
70. Chernik DA, Cochrane C, Mendels J: Effects of lithium carbonate on sleep. *J Psychiatr Res* 1974; 10:133-146
71. Monti JM: Catecholamines and the sleep-wake cycle, II: REM sleep. *Life Sci* 1983; 32:1401-1415
72. Bowker RM: Waking PGO waves: largest amplitudes occur only during alerting reactions, not high arousal levels, in *Modulation of Sensorimotor Activity During Alterations in Behavioral States*. Edited by Bandler R. New York, Alan R Liss, 1984
73. Bowker RM: Variability in the characteristics of pontogeniculooccipital spikes during paradoxical sleep. *Exp Neurol* 1985; 87:212-224
74. Morrison AR: Brainstem regulation of behavior during sleep and wakefulness, in *Progress in Psychobiology and Physiological Psychology*, vol. 8. Edited by Sprague JM, Epstein AN. New York, Academic Press, 1979
75. Glenn LL: Brainstem and spinal control of lower limb motoneurons with special reference to phasic events and startle reflexes, in *Brain Mechanisms of Sleep*. Edited by McGinty DJ, Drucker-Colin R, Morrison A, et al. New York, Raven Press, 1985
76. Drucker-Colin R, Bernal-Pedraza J, Fernandez-Cancino F, et al: Increasing PGO spike density by auditory stimulation increases the duration and decreases the latency of rapid eye movement (REM) sleep. *Brain Res* 1983; 278:308-312
77. Davis M: The mammalian startle response, in *Neural Mechanisms of Startle Behavior*. Edited by Eaton RC. New York, Plenum, 1984
78. Burstein A: Dream disturbances and flashbacks (letter). *J Clin Psychiatry* 1984; 45:46
79. Sonnenberg SM: Introduction: the trauma of war, in *The Trauma of War: Stress and Recovery in Viet Nam Veterans*. Edited by Sonnenberg SM, Blank AS Jr, Talbott JA. Washington, DC, American Psychiatric Press, 1985
80. Maron L, Rechtschaffen A, Wolpert EA: Sleep cycle during napping. *Arch Gen Psychiatry* 1964; 11:503-508
81. Webb WB, Agnew HW Jr: Sleep cycling within twenty-four hour periods. *J Exp Psychol* 1967; 74:158-160
82. Karacan I, Finley WW, Williams RL, et al: Changes in stage 1-REM and stage 4 sleep during naps. *Biol Psychiatry* 1970; 2: 261-265
83. Carskadon MA, Dement WC: Distribution of REM sleep on a 90 minute sleep-wake schedule. *Sleep* 1980; 2:309-317
84. Fiss H: Current dream research: a psychobiological perspective, in *Handbook of Dreams*. Edited by Wolman BB. New York, Van Nostrand Reinhold, 1979
85. Krystal JH, Giller EL Jr, Cicchetti DV: Assessment of alexithymia in posttraumatic stress disorder and somatic illness: introduction of a reliable measure. *Psychosom Med* 1986; 48:84-94
86. Hefez A, Metz L, Lavie P: Long-term effects of extreme situational stress on sleep and dreaming. *Am J Psychiatry* 1987; 144: 344-347
87. Freud S: *New introductory lectures on psycho-analysis* (1933)

- [1932]), in *Complete Psychological Works*, standard ed, vol 22. London, Hogarth Press, 1964
88. Fenichel O: *The Psychoanalytic Theory of Neurosis*. New York, WW Norton, 1945
 89. Moses R: Adult psychic trauma: the question of early predisposition and some detailed mechanisms. *Int J Psychoanal* 1978; 59:353-363
 90. Vogel GW, Voegel F, McAbee RS, et al: Improvement of depression by REM sleep deprivation—new findings and a theory. *Arch Gen Psychiatry* 1980; 37:247-253
 91. Keane TM, Kaloupek DG: Imaginal flooding in the treatment of post-traumatic stress disorder. *J Consult Clin Psychol* 1982; 50: 138-140
 92. Blanchard EB, Kolb LC, Pallmeyer TP, et al: A psychophysiologic study of post-traumatic stress disorder in Vietnam veterans. *Psychiatr Q* 1983; 54:220-228

Psychiatry in Africa: An Overview

Adebayo Olabisi Odejide, M.D., Lamidi Kolawole Oyewunmi, M.D.,
and Jude Uzoma Ohaeri, M.D.

The authors review the practice of psychiatry in Africa today. They describe the similarities as well as the differences between psychiatry in Africa and in the Western world in the rates, presentations, and treatment of neurosis, depression, schizophrenia, and suicide and drug- and alcohol-related problems. Child psychiatric services and research in biological psychiatry are rare in Africa, and sociocultural problems confront epidemiologic studies and the use of psychotherapy. The authors conclude that to achieve the goal of mental health care for all Africans, psychiatry should be included in the primary health care program, regional postgraduate medical centers are needed, and a means of gathering statistics and funding research should be fostered.

(Am J Psychiatry 1989; 146:708-716)

Africa, the second largest and most tropical continent, with a population of about 350,000,000, is a land of some 53 independent, multiracial nations (1). In the face of such diverse cultures even within nations (e.g., Nigeria has at least 240 different ethnic languages), can there be common threads within the fabric of the state of psychiatry today, and can this commonality become the basis for concerted action to ensure effective mental health care on the continent by the year 2000? If the discussion of this goal were focused on a unique African psychiatry, it would be impractical, but if the discussion is focused on the history of psychiatry in Africa, the clinical patterns, and the problems militating against mental health care research and delivery, then it should be possible to show interesting continental trends. This paper intends to do just that.

The common trends appear to have been made possible by the similar experiences of all African nations in the political, social, economic, and cultural realms. For instance, all have recently undergone devastating colonial experiences. By the time Western European co-

lonialists left Africa in the 1960s, serious developmental problems had been created that affected all areas of endeavor, especially health care (2). The ever-present fear of military coups and the distracting power of apartheid in South Africa have helped to rob Africa of the kind of stable atmosphere in which well-thought-out health policies could be executed.

Economically, excluding the Republic of South Africa, the estimated total industrial manufacturing output of Africa is a meager 12% of the gross domestic product, and its population growth rate is high (about 3%) compared with Europe's (about 1%) (3). This places African nations firmly in the developing world, which has serious implications for health care delivery. More than 44% of the population are under the age of 15, and unemployment and undernutrition are rife.

Socioculturally, most Africans, regardless of their level of education, adhere in varying degrees to a belief in supernatural causation of disease. This popular belief system affects psychiatric symptoms and health-seeking behavior.

Confronted with the problems of hunger and the need to supply pure water, to eradicate preventable infectious diseases, to provide better education, and to improve the basic standard of living, health planners in the Third World in general and Africa in particular have until recently tended to limit the scope of mental health action to mental hospitals with mainly custodial functions (4). However, recent developments, such as the successful promotion by the World Health Organization (WHO) of the ideals of primary health care for all by the year 2000, collaborative research on strategies for extending mental health in rural areas, and various other research endeavors, seem to have helped to produce a change of heart in favor of mental health care among African health planners. As various African governments prepare to expand their mental health care services to meet the ideals of WHO, the time seems ripe to take a global look at psychiatry in Africa and to highlight the problems of this specialty today and the strategies for meeting these ideals.

German (5-7) attempted such an overview, but he was concerned with "Sub-Saharan Africa," excluding the Republic of South Africa. To present a more comprehensive picture, in this paper we will review the existing literature and will portray the mental health care scene in representative countries from five regions: 1) Arab-Berber North Africa, represented by

Received Dec. 4, 1987; revision received Aug. 9, 1988; accepted Nov. 3, 1988. From the Department of Psychiatry, University College Hospital, Ibadan. Address reprint requests to Dr. Odejide, Department of Psychiatry, College of Medicine, University College Hospital, Ibadan P.M.B. 5116, Nigeria.

Copyright © 1989 American Psychiatric Association.

comparatively liberal Egypt, more conservative Morocco, and Sudan, which has a mixed Arab Muslim and Negro Christian population, 2) predominantly pure Negro West Africa, represented by Nigeria and Senegal, 3) Negro Central Africa, represented by Uganda, 4) Swahili-Bantu Negro East Africa, represented by Kenya and Zambia, and 5) Bantu Negro South Africa, represented by the Republic of South Africa.

In a way, the fact that such a review is possible could be seen as the result of the successful campaign for the promotion of psychiatry by such founding fathers as the late Henri Collomb in Senegal, Tigani El-Mahi in Sudan, and Lambo in Nigeria. It is also the result of the presence of high-quality journals devoted to African and Arab health issues, principal among which are *Psychopathologie Africaine*, published in Senegal; the *East African Medical Journal*, published in Kenya; the *West African Journal of Medicine* and the *African Journal of Medical Sciences*, published in Nigeria; the *South African Medical Journal*, published in the Republic of South Africa; the *Annals of Saudi Medicine*, formerly *King Faisal Specialist Hospital Medical Journal*, published in Saudi Arabia; and the *African Journal of Psychiatry*, published in Lagos, now temporarily out of print.

AFRICAN TRADITIONAL MEDICINE AND SYNCRETIC CHURCHES

The terms "traditional" medicine and "folk" medicine as used here refer to indigenous systems of traditional healing, characteristic of what were essentially nonliterate peoples of Africa, Asia, and the Americas (8). These are the nonformalized traditions of healing, in contrast to the ancient codified medical systems of nations such as Saudi Arabia (*unani-tibbi*), India (e.g., *ayurveda*), and China (e.g., acupuncture). Several reports (9–13) indicate that the beliefs underlying the practice of traditional medicine across Africa are similar. Supernatural causes, such as witchcraft, a human curse, or offenses against the gods or ancestors, are commonly sought for mental disorders.

Traditional healers are popular and easily available to all. Among the Senegalese they are called *marabouts* (specialists in magic, divination, and the supernatural). They are generally divided into herbalists (*onisekun* among the Yoruba of Nigeria) and diviners or priests (*babalawo* among the Yoruba). The description by El-Islam (14) of traditional medical beliefs among the Arabs is particularly interesting because it applies to black Africa as well. He noted,

The most important of such beliefs relate to supernatural agents such as the devil, jinn, sorcery and the evil eye. Unacceptable wishes, feelings and acts are liable to be projected onto the devil and ruminations involving aggressive or unacceptable sexual impulses are also attributable to him, enabling people to doubt or to disavow these and to

avoid guilt feelings respecting them—such ideas are the devil's, not one's own In consequence, charms against the evil eye are frequently found, and there are numerous rituals which are followed in the hope of gaining protection against the evil eye or sorcery or both. (p. 6)

Traditional medicine men recognize the broad group of mental disorders that modern psychiatrists deal with (15), but their methods consist mainly of the use of herbs, incantations, and divinations, and their demographic characteristics suggest that they are aging. Prince (16) identified *Rauwolfia serpentina* as one of the herbs used by the native healers who specialize in treating mental illness.

In short, before colonial times, Africa had an established system of health care that included the recognition and management of the mentally ill and was provided by traditional healers. Today, because of their ready availability and accessibility and the virtual absence of modern medical care in the rural areas of Africa, there have been popular appeals for the integration of traditional healers into the health care delivery system. Such an attempt was once made in Ghana with modest success (17), and the services of such healers have been used on a limited basis by one eminent Nigerian psychiatrist (18).

One of us (J.U.O.) (19) has made the point that the beliefs and practices of these healers are not unique to Africans or to other peoples of developing countries; rather, they represent the stage in racial evolution at which the white man met them. The peculiarly harsh colonial experience has not made it easy to transcend beliefs in supernatural causes of illness in the three decades of colonization, during which time Europe leapt through the industrial to the jet age. African scholars with impeccable credentials have investigated these healers, but they have done so as outsiders because none has been a *marabout* or an *onisekun* or a *babalawo*. The intimate details of the practices of these healers are therefore still shrouded in secrecy. Most of the healers are illiterate, their clinical skills remain stagnant, and they do not seem to have benefited from years of apparent interaction with scientists. As the society becomes more educated, it is useful for the thinking people of Africa to wonder what will happen to the rich cultural heritage represented by the traditional healers, especially as the society loses its belief in the supernatural. One of us (J.U.O.) (19) has suggested that national research associations incorporating the traditional healers should be formed, that the medicinal plants of Africa should be gathered and studied, and that traditional medicine should be codified or formalized—using as a starting point the highly respected and widely diffused *ifa* method of divination (20).

A related indigenous system of care for the mentally ill these days in Africa is the syncretic or independent churches. Ndiokwere (21) has given a good description of the evolution of these churches in modern black Africa. In these syncretic churches, Western religious

beliefs have been transformed by the unique African temperament, resulting in a hybrid that seems closer in content to the religion of African culture. This is a neglected area of research. An overwhelming number of our people (especially the mentally ill) throng to these churches for healing. The so-called healers in these churches foster beliefs in the supernatural, and these beliefs often create problems in managing patients in hospitals. Thus, it is imperative that academic interest be focused on these churches. In a typical psychiatric clinic, at least in black Africa today, the usual picture of health-seeking behavior is that the patient starts with a traditional healer, then is taken to a syncretic church for prayers or miraculous healing as the symptoms worsen, and then, as the illness remains unabated, is brought to a hospital (22). After effective hospital treatment, the patient typically still maintains strong links with the alternative systems of care (23).

EPIDEMIOLOGY OF PSYCHIATRIC DISORDERS

Earlier Western workers in Africa, such as Carothers (24), were impressed by the picture of the African as a happy savage who was not responsible enough to experience the psychic conflicts associated with mental disorders. They reported that mental ill health in general and depression in particular were uncommon in the African (6, 7). It was therefore surprising to hear of the work of Giel and Van Lujik (25) in Ethiopia; they reported in 1969 that in most of the health centers studied, mental disorders were more often diagnosed than the apparently ubiquitous infectious diseases for which Africa was better known.

Several methodologically sound studies conducted since the 1960s (the decade of independence for most African countries) have consistently shown that most neurotic and psychotic disorders are as common in rural and urban Africa as in comparable areas in the Western world. For instance, cross-cultural epidemiologic studies by researchers with anthropological backgrounds have been conducted in rural Nigeria (compared with Nova Scotia) (26) and rural Uganda (compared with London) (27). These studies used standard instruments such as the Present State Examination and the Cornell Medical Index.

WHO has sponsored studies aimed at highlighting strategies for extending mental health care in rural areas of nine developing countries, including Sudan in North Africa and Senegal in West Africa (28–30). Preliminary findings of these WHO studies showed that a significant proportion of patients seeking primary care had mental disorders, most of them neurotic, and that communities were aware of serious mental disorders and their harmful effects (31).

In a study of the rural Serer community in Senegal, Beiser et al. (32) found that it was possible to develop a standardized instrument for gathering data about psychiatric illness in an illiterate culture. They found that the Serer's "illness of the spirit" and the psychia-

trist's psychiatric disorder were "roughly the same kinds of things." More localized reports from Egypt (33), Northern Sudan (34), Uganda (5), Kenya (unpublished paper by S.G. Gatere), other parts of East Africa (35), and Nigeria (36, 37) have also shown that mental disorders constitute a common cause of morbidity in general hospitals in urban and rural Africa.

In spite of the fact that such problems as diarrhea, other infectious diseases, and malnutrition occupy a primary place in health care planning for childhood disorders, substantial childhood psychiatric disorders have been highlighted in Africa. For example, as part of WHO's collaborative study on strategies for extending mental health care, Giel et al. (38) reported on the prevalence of mental disorders in patients who were younger than 15 years at primary health care centers. They found rates comparable to those in the Western world. Diop et al. (39), using a similar methodology in another rural area of Senegal, found that 17% of 545 children aged 5–15 years were suffering from some form of emotional problem, behavior disturbance, or neuropsychiatric disorder. Similar findings have been made among children in Ethiopia (40) and Sudan (41). In addition, children attending psychiatric services in Nigeria (42) and Uganda (43) showed a wide range of diagnoses. German's review of the prevalence of psychiatric morbidity among pregnant African women (6, 7) found widely reported rates higher than those found in Europe.

The matter in dispute in cross-cultural research is not the substantial prevalence of mental disorders in Africa. Rather, the literature shows that there is a need to clarify the nature and prognosis of somatization, depression, and schizophrenia and the prevalence of suicidal behavior and alcohol-related problems in comparison with their presentations and prevalence in the Western world. It seems to be in these nosological entities that psychiatric phenomenology in Africa differs somewhat from the situation in the West, and they therefore require some discussion. Particular reference should also be made to the way the Arabic taboo on sex has affected psychiatric symptoms and health-seeking behavior, especially among Arab women. Many workers from the Arab world (14, 34, 44) have stressed this point.

DIAGNOSING AND TREATING DEPRESSION IN AFRICA

Excellent reviews of depression across cultures with special reference to Africa have been done by Prince (45), Rwegellera (46), and Weiss and Kleinman (47). Prince (45) reviewed 14 reports published between 1895 and 1957 that discussed depression in Kenya, South Africa, Nigeria, Tanzania, and Ghana. Nearly all of the papers up to 1955 pointed to a difference between Western and African patients in the presentation and prevalence of depression. Most studies were in agreement that guilt feelings, self-deprecation, se-

were retardation, and associated suicidal behavior were far less prevalent in Africa than in the Western world. Rwegellera (46) agreed with this trend but noted exceptional cases such as his own findings in Zambia, where depression of the type seen in the West was commonly diagnosed among hospital patients. Weiss and Kleinman (47), on the other hand, noted with surprise that earlier reviews of African studies ignored the import of the findings of Field (48), an anthropologist and psychiatrist, in Ghana. Field investigated the native healing shrines of rural Ghana and found that not only was depression common but guilt feelings were also commonly expressed, especially in relation to witchcraft. Weiss and Kleinman (47) concluded that earlier Western workers failed to recognize depression in Africans because the Western conception of depression implied a high level of personality development and sense of responsibility, which the colonialists were not ready to admit that Africans could have. El-Islam (14) noted,

Affective disorders among Arabs have been reported to show a low incidence of undisguised affective symptoms in both depressive and manic forms. Guilt feelings have been reported to be rare in depressed Arab patients. One study found that if depressed patients are allowed to elaborate on their feelings beyond the somatic facade, guilt feelings could be demonstrated in many especially among the educated. The clinical picture of depression in the urbanized Arab is approaching that in the West, a finding which is not surprising. (p. 10)

Although large reviews continue to show the relative uncommonness of the more severe symptoms of depression, isolated works from various countries using rigorous methodology have shown the commonness of the core symptoms of depression among hospital patients in Africa. For instance, in 1983, Majodina and Johnson (49), using a standardized instrument for the assessment of depressive disorders in Accra, Ghana, found that 76%–100% of their patients reported a core of depressive symptoms, namely, sadness, depressed mood, joylessness, inability to enjoy, hopelessness, anxiety and/or tension, lack of energy, disruption of social functioning, lack of self-confidence, loss of interest, and loss of ability to concentrate.

German (6, 7) was particularly impressed by the epidemiologic study in 1979 of Orley and Wing (27) in rural Uganda, which used the Present State Examination to compare the prevalence and types of depression in Uganda with those in London. Similarity was found in the pattern of depression. In 1982, Paes et al. (50), after reviewing the case notes of Moroccans admitted for confirmed mania to the Ar-Razi Hospital in 1980, found no fundamental differences in the clinical expression of manic-depressive psychosis in Morocco compared with that described in Europe. However, cross-cultural studies, such as those of Guelfi et al. (51) (comparing Maghrebians and French inpatients), Hanck et al. (52) (comparing Senegalese and Spanish inpatients), and Ammar et al. (53) in the Maghreb

(Morocco, Algeria, and Tunisia), have clearly indicated the preponderance of somatization symptoms among African patients with depressive disorders and a preponderance of psychological symptoms among Western patients.

There is no doubt concerning the predominance of somatization symptoms among Africans, but somatization is not unique to Africans. The general thinking in African psychiatry is that depression is often equivalent to somatic complaints (54–56). Reporting from the Republic of South Africa, Gillis (57) noted that “although manifestations of depression as described in the textbooks are rare, depression is common, but one must not look for it in terms of feelings of guilt and self-reproach and retardation. Feelings of sadness, hypochondriasis, and somatization are more characteristic features.” Binitie (58) came to the same conclusion after reviewing the literature from the Nigerian perspective.

But what is the nature of these somatized symptoms? First, they present as paresthesias (crawling, heat, peppery sensations, numbness, and vague aches and pains all over the body) quite different from the type reported in the Western literature (59). Second, although the Yoruba of Nigeria, for instance, refer to the heart or abdomen when they are indicating that they are depressed, these somatization symptoms do not refer to the heart or tummy—thus casting doubt on the popular suggestion that somatization is common because the dialect of various African tribes does not accommodate depression as a concept. Third, unpublished data from the work of Ohaeri and Olatawura are in keeping with the widely held clinical impression that patients with somatic symptoms do not respond to physical methods of treatment, including sufficient doses of tricyclic antidepressants. Another interesting feature of affective disorders in Africa is the finding of Makanjuola (60) that mania, at least among the Yoruba Nigerians, tends to be unipolar, which is different from the classical Western picture.

SCHIZOPHRENIA AND ACUTE PSYCHOTIC STATES

In view of the wide disparity in the availability of health care facilities in Africa and the Western world, the finding by the International Pilot Study of Schizophrenia that, over a period of 2 years, schizophrenic patients from the Third World had better outcomes than those from the developed nations was surprising. (Ibadan, Nigeria, was a center in this study.) In view of the widely reported prevalence of acute short-lived psychotic states in Africa (6, 7), it is arguable whether the results would have been the same if the investigators had used *DSM-III* criteria to diagnose schizophrenia. The available literature shows that the International Pilot Study of Schizophrenia finding lends support to findings of trends in schizophrenia outcome that have been noted by earlier workers. Lamont and Blignault (61), in a study of 258 male Bantu patients

admitted on certification to a psychiatric hospital in 1952, noted that "mental disorder in the male Bantu is far from being the chronic and permanently incapacitating condition that it is commonly considered to be." Okasha et al. (33), reporting on a study done in Egypt, noted that schizophrenic patients from the countryside had an acute onset and a better response to treatment and did not become chronically ill, "most probably because of the protective nature of the family surroundings and the cohesion of the community among such classes." With regard to the influence of the family in schizophrenia, the protective influence of the extended family system, for which Africa is noted, has been highlighted by El-Islam (14). In India, Wig et al. (62) have shown that a likely factor in the better outcome of schizophrenia in the Third World is a more tolerant and less critical home environment.

If that be the case, then once again the thinking people of Africa will need to ponder on the already visible impact of urbanization, industrialization, and education on the extended family system. The large number of psychotic vagrants who roam the streets of Africa testify to the fact that health planners need to give serious attention to issues of rehabilitation.

Another interesting feature of schizophrenia in Africa is the commonness of the catatonic forms (33, 63), presentations that are said to be rare today. Many of the patients with catatonic schizophrenia whom we see in clinical practice are quite well fed and of middle-class background.

SUICIDAL BEHAVIOR AND DRUG- AND ALCOHOL-RELATED PROBLEMS

The general indication is that suicide in Africa is far less prevalent than it is in developed nations (6, 7, 64). The rate of suicide is also reported to be low among Negroes worldwide (65). However, Rwegellera's finding (66) of a relatively high suicide rate in Lusaka, Zambia, is noteworthy. In a study of all open verdicts of suicide in Lusaka in 1967-1971, Rwegellera found a rate of 12.8 per 100,000 per year for all Africans older than 14 years, compared with a rate of 20.9 for all European residents of Lusaka. A suicide rate of 7.0 was found among the Basoga of Uganda (6). Considering the particularly low rates of 0.7 found in Nigeria (67) and 0.8 in Senegal (6, 7), we could conclude that although suicidal behavior is far less prevalent in Africans compared with Caucasians, the rates in East Africa are higher than those in West Africa.

A similar trend is also noticeable in the case of alcohol-related problems. Although substantial alcohol-related problems have been highlighted in Africa (unpublished 1988 paper by A.O. Odejide and J.U. Ohaeri), the prevalence rate is much lower than that reported in developed countries. In the countries of East and South Africa, however, alcohol-related problems constitute visible problems to the economic and health sectors (61, 66, 68). In North African countries,

although the value of Islam in restricting the use of alcohol is extolled, rates of alcohol-related problems (unpublished 1987 paper by El-Tigani Hammad) are far higher than those reported for the permissive society of Southern Nigeria (69), for instance. This reminds us of the dangers of secret drinking, which Tigani El-Mahi (70) has highlighted, in societies that call for total abstinence.

AVAILABILITY AND USE OF PSYCHIATRIC SERVICES

The ethics and standards of scientific medicine are not new to Africa. By 1285, they were rigorously pursued in Egypt. At that time the Al-Mansuri Hospital was established in Cairo by Sultan Al-Mansuri Qalanwun (71). In spite of this long contact with the ethos of science, the state of psychiatric care in Africa in general is poor indeed, except for whites in the Republic of South Africa. Psychiatric services for whites in South Africa, described in 1979 by Gills (72) and in 1978 by Levin (73), is excellent. Under apartheid, however, the services for blacks in South Africa are minimal. For example, the Weskoppies Mental Hospital has about 900 beds for male Bantu patients, most of whom are admitted patients on certification. In 1953, Lamont and Blignault (61) said that "other types of admission were few in number." By 1978, the situation of mental health care for blacks seemed to have deteriorated even more, as attested to by a preliminary review by the WHO Secretariat, published in *Psychopathologie Africaine* (74). The WHO paper stated that "between 8,000 and 9,000 Africans suffering from mental disorders are detained against their will in privately owned institutions in the Republic of South Africa," and that there was "not a single Black psychiatrist." By 1979, when the society of psychiatrists of South Africa discussed the issue of psychiatry for Africans (75), there were still no black psychiatrists in South Africa, although a medical school has now been established with admission policies favoring blacks (76). In the face of this obviously deliberate neglect on the part of the government and the low acceptability and utilization of available health services, Mankazana (77) has made a case for the traditional healer in South Africa.

In the rest of Africa, the situation for psychiatry seems best in Egypt and Nigeria, at least in terms of number of native psychiatrists and the degree of sophistication in the field. Moreover, these two countries have some economic and industrial power and have well-established postgraduate medical training programs. There are some differences between East and South Africa on the one hand and West Africa on the other in terms of methods of bringing patients to the hospital and the size of psychiatric institutions.

With Zambia as a focus, Dhadphale and Shaikh (78) and Rwegellera (79) have provided insight about East African psychiatry. About 65% of all patients brought to the hospital to see a psychiatrist in Uganda in 1 year were under security escort, and in Zambia 58% of the

patients were brought by the police. According to Dhadphale and Shaikh (78), "this is to be expected since the two countries operate under similar mental health acts . . . and are largely Bantu." In Zambia, which has a population of 5.5 million, there are large psychiatric hospitals with few psychiatrists and the psychiatric units in general hospitals also have a large number of beds but only one or two psychiatrists. For example, the Chainama Hill Psychiatric Hospital has an official capacity of 420 beds and only six psychiatrists (79), and the psychiatric unit of Ndola General Hospital has facilities for 180 psychiatric patients and two psychiatrists (78). There is extensive use of medical auxiliaries who have had a 3-year course in mental disorders after 10–12 years of general education. We have already noted that the Weskoppies Mental Hospital in South Africa has facilities for 900 male Bantus.

In West Africa and parts of the Arab North the situation is quite different. In Nigeria, for instance, which had a population of more than 80 million at the time of Rwegellera's report, psychiatric practice was firmly in the hands of natives. There were about 50 psychiatrists, most of them in the south. The largest psychiatric hospital (the Aro Neuropsychiatric Hospital in Abeokuta) had an official capacity of 200 (excluding the Lantoro Annexe, initially for the criminal insane). The oldest teaching hospital at Ibadan had only nine beds for psychiatric patients but six psychiatrists. (By mid-June 1988, this teaching hospital's psychiatric beds were increased to a record 32, with an annexed detoxification unit that also had 32 beds.) In Nigeria, it is quite unusual for patients to be brought by the police, and there are no psychiatric medical auxiliaries like those described for Zambia.

Collomb (80), in describing the state of psychiatry for French West Africa, noted a paucity of psychiatric beds. In 1975, the time of his report, most French West African countries had no psychiatrists and no psychiatric hospitals, with the exception of Senegal, where services were comparatively well developed. The neuropsychiatric hospital in Dakar, built in 1956, was for 100 inpatients. In Upper Volta, a ward for psychiatric patients in a general hospital had capacity for 80 beds. In Cameroon, one hospital in Yaounde was for 80 beds and another in Duala was for 50 beds. In Benin Republic (then Dahomey), a center was being planned. In Ivory Coast, a psychiatric hospital at Bingerville had capacity for 250 beds. In Niger, a ward was created in a general hospital in Niamey with 80 beds. According to recent reports, the situation does not seem to have improved much. In 1983, Coulibay et al. (81) stated that a ward in a general hospital "still constitutes the only facility for psychiatric care in Mali," and in 1980, Osouf (82), writing about Niger, described "the increasingly bad conditions of the assistance to mentally ill people in this country."

As an example of the situation in Arab North Africa, excluding Egypt, El-Tigani Hammad (unpublished 1987 paper) noted that in Sudan, the only psychiatric

hospital in the country (Tigani El-Mahi Psychiatric Hospital), opened in 1973, has capacity for 100 beds.

Except in the Republic of South Africa, mental health staff such as trained social workers and clinical psychologists are even more scarce than psychiatrists. In spite of the fact that substantial childhood psychiatric disorders have been highlighted, child psychiatric services are rare. However, psychiatric nurses are being trained in large numbers, and it is hoped that they will be able to serve as community psychiatric nurses at the primary health care level. Clinical psychology is also attracting graduates in Nigerian and Ghanaian universities, and—judging by their academic publications—we think that the few clinical psychologists are really distinguishing themselves.

The future looks bright for psychiatry. In Nigeria, a department of medical social work is being planned at the University of Ibadan in collaboration with a university in the United States. Full-fledged postgraduate medical training programs have been started in Nigeria, Egypt, and Kenya, and it is hoped that they will be able to attract medical graduates. In addition, the West African Postgraduate Medical College, with centers in Ghana and Nigeria, caters to the training needs of many West African countries. In view of the continuing economic hardship being experienced in Africa and the difficulty of sending students overseas for training, agencies such as the Organization of African Unity and WHO will need to look into the possibility of sponsoring medical graduates to train in psychiatry at the available centers in Africa. Under such a scheme, some East African doctors have received training in Nigeria.

TREATMENT METHODS

The literature (33, 34, 72, 73, 79, 83, 84) shows that modern Western methods of treatment are used by African psychiatrists. Psychotropic drugs and ECT are the most commonly used methods. Because of the shortage of anesthetic personnel and equipment, however, ECT is usually administered without anesthesia (85). In the face of the overwhelming number of patients and the few psychiatrists, formal insight-oriented psychotherapy is not a common feature of psychiatric practice, but supportive psychotherapy is often applied. Formal psychotherapy as practiced in the West has social and cultural limitations in Africa, in view of the popularity of supernatural beliefs, the tendency to project rather than introspect, the patient's expectations of the physician, and some socioeconomic factors that have been highlighted by Olatuwura (86). The techniques of behavior modification are being applied by clinical psychologists (87).

PROBLEMS OF RESEARCH

Odejide and Acuda (unpublished 1986 paper) have lamented the fact that most studies from Africa are

descriptive and that studies in biological psychiatry are rare. The foreign pharmaceutical companies prefer that Africa be a marketing target rather than a source of drug trials. Serious socioeconomic and cultural factors limit biological and longitudinal psychiatric studies in Africa. These factors include lack of funding, lack of the relevant technological instruments, illiteracy, poor record keeping, unreliable vital statistics, and an unstable political climate. As the literacy rate improves and more political stability is achieved, it is hoped that these limitations to research will be overcome. Africans need to promote the development of statistics and research funding.

STRATEGIES FOR IMPROVING MENTAL HEALTH CARE DELIVERY

Strategies for promoting mental health care should, of course, be pursued at the primary, secondary, and tertiary levels of prevention. Toward this end, there is no shortage of ideas on alternative systems of care in Africa (88–90). One that has been actively promoted in Nigeria by Lambo, in Senegal by Henri Collomb, and Sudan by Tigani El-Mahi is the village system of care (91). This has obvious limitations today, with increasing patient sophistication and dwindling resources at the village level.

Although no single system of care can be prescribed for Africa, it will be worthwhile to pay particular attention to the findings and suggestions of the WHO collaborative study on strategies for extending mental health care in primary health care settings. Psychiatry will need to be incorporated into the primary health care scheme (92).

CONCLUSIONS

Aubrey Lewis (93) was obviously correct in stating that “there is no convincing evidence that the etiology and pathology of the varieties of mental disorder is different in Africans from what it is in Europeans . . . and the basic principles of psychiatry seem to be of universal application.”

The subtle differences between Western and African psychiatry highlighted in this paper—in terms of symptoms and in the availability and use of services—point to the direction in which teachers, researchers, and health planners in Africa should lay due emphasis. The problems confronting psychiatric practice and research are such that we need collaboration with our more favored Western colleagues. Such collaboration would improve world psychiatric knowledge and promote international scientific business.

Although difficulties endure, African psychiatrists should become creative in the circumstance rather than despair. For instance, we need to study how the healthy aspects of the traditional culture can be adapted to formulate appropriate psychotherapy. In

this way, our many patients with somatization who do not respond to physical methods of treatment will be helped.

The promotion of mental health at the primary level of prevention should include health education intelligently focused on those aspects of traditional beliefs which have adversely affected health-seeking behavior. Some form of cooperation will have to be established with the providers of alternative systems of health care, and research in traditional medicine should help to improve their clinical skills and economic status. Meanwhile, the body of evidence on psychiatric morbidity is convincing enough to warrant increasing the period of psychiatric teaching in undergraduate training and incorporating psychiatry into the primary health care scheme.

REFERENCES

1. Uwechue R (ed): *Africa Today*, 1st ed. London, African Journal, Kirkman House, 1981
2. Rodney W: *How Europe Underdeveloped Africa*. London, Bogle-L'Ouverture Publications, 1972
3. Africa, in *The New Encyclopaedia Britannica*, vol 13, *Macropaedia: Knowledge in Depth*. Chicago, Encyclopaedia Britannica, 1985
4. Wig NN, Suleiman MA, Routledge R, et al: Community reactions to mental disorders: a key informant study in three developing countries. *Acta Psychiatr Scand* 1980; 61:111–126
5. German GA: Aspects of clinical psychiatry in Sub-Saharan Africa. *Br J Psychiatry* 1972; 121:461–479
6. German GA: Mental health in Africa, I: the extent of mental health problems in Africa today. *Br J Psychiatry* 1987; 151: 435–439
7. German GA: Mental health in Africa, II: the nature of mental disorder in Africa today, some clinical observations. *Br J Psychiatry* 1987; 151:440–446
8. Good CM, Hunter JM, Katz SH, et al: The interface of dual systems of health care in the developing world: toward health policy initiatives in Africa. *Soc Sci Med* 1979; 13D:141–154
9. Jahoda GC: Traditional healers and other institutions concerned with mental illness in Ghana. *Int J Soc Psychiatry* 1961; 7:245–268
10. Otsyula WC: Native and Western healing: the dilemma of East African psychiatry. *J Nerv Ment Dis* 1973; 156:297–299
11. Imperato PJ: Traditional medical beliefs and practices in the city of Timbuctoo. *Bull NY Acad Med* 1976; 52:241–252
12. Edgerton RB: Traditional medicine for mental illness in Africa: an overview. *Cult Med Psychiatry* 1980; 4:167–189
13. Odejide AO: Traditional (native) psychiatric practice: its role in modern psychiatry in a developing country. *Psychiatr J Univ Ottawa* 1979; 4:297–301
14. El-Islam MF: Overview: Arabic cultural psychiatry. *Transcultural Psychiatric Research Rev* 1982; 19:5–23
15. Prince R: Indigenous Yoruba psychiatry, in *Magic, Faith and Healing*, 2nd ed. Edited by Kiev A. New York, Free Press, 1966
16. Prince R: The use of *Rauwolfia* for the treatment of psychoses by Nigerian native doctors. *Am J Psychiatry* 1960; 117:147–149
17. Warren DM, Bora GS, Tregoning MA, et al: Ghanaian national policy toward indigenous healers. *Soc Sci Med* 1982; 16:1873–1881
18. Lambo TA: The village of Aro. *Lancet* 1964; 2:513–514
19. Ohaeri JU: African traditional medicine: a stage in the people's history. *African Notes* (in press)
20. Bascom W: *Ifa Divination: Communication Between Gods and Men in West Africa*. Bloomington, Indiana University Press, 1969
21. Ndiokwere IN: *Prophecy and Revolution: The Role of Prophets*

- in the Independent African Churches. London, SPCK, Holy Trinity Church, 1981
22. Jegede RO: A study of the role of socio-cultural factors in the treatment of mental illness in Nigeria. *Soc Sci Med* 1981; 15A: 49-54
 23. Ebigho PO, Tyodzua W: Healing methods of a prayer house in Nigeria, in *Mental Health in Africa*. Edited by Erinosh O A, Bell NW. Ibadan, Nigeria, Ibadan University Press, 1982
 24. Carothers JC: A study of mental derangement in Africans and an attempt to explain its peculiarities, more especially in relation to the African attitude to life. *J Ment Sci* 1947; 93:548-597
 25. Giel R, Van Luijk JN: Psychiatric morbidity in a small Ethiopian town. *Br J Psychiatry* 1969; 115:149-162
 26. Leighton AM, Lambo TA, Hughes CC, et al: *Psychiatric Disorders Among the Yorubas*. Ithaca, NY, Cornell University Press, 1963
 27. Orley J, Wing JK: Psychiatric disorders in two African villages. *Arch Gen Psychiatry* 1979; 36:513-520
 28. Harding TW, de Arango MV, Baltazar J, et al: Mental disorders in primary health care: a study of their frequency and diagnosis in four developing countries. *Psychol Med* 1980; 10:231-241
 29. Sartorius N, Harding TW: The WHO collaborative study on strategies for extending mental health care, I: the genesis of the study. *Am J Psychiatry* 1983; 140:1470-1473
 30. Harding TW, Busnello E, Climent CE, et al: The WHO collaborative study on strategies for extending mental health care, III: the evaluative design and illustrative results. *Am J Psychiatry* 1983; 140:1481-1485
 31. Harding TW, Climent CE, Collignon R, et al: Mental health and primary care: first results of a WHO concerted study. *Psychopathologie Africaine* 1979; 15(1):5-28
 32. Beiser M, Ravel J, Collomb H, et al: Assessing psychiatric disorder among the Serer of Senegal. *J Nerv Ment Dis* 1972; 154: 141-151
 33. Okasha A, Kamel M, Hassan AH: Preliminary psychiatric observations in Egypt. *Br J Psychiatry* 1968; 114:949-955
 34. El-Sarrag ME: Psychiatry in the Northern Sudan: a study in comparative psychiatry. *Br J Psychiatry* 1968; 114:945-948
 35. Kagwa BH: Observations on the prevalence and types of mental disease in East Africa. *East Afr Med J* 1965; 42:673-683
 36. Jegede RO, Bamgboye EA, Ohaeri JU: Preliminary report of the Ibadan depression project. *West Afr J Med* 1984; 3(1):25-30
 37. Mbanefo SE: The general practitioner and psychiatry, in *Report of the First Seminar/Workshop on Psychiatry and Mental Health Care in General Practice*. Edited by Olatawura MO. Ibadan, Nigeria, University of Ibadan, Department of Psychiatry and Neurology, 1971
 38. Giel R, de Arango MV, Climent CE, et al: Childhood mental disorders in primary health care: results of observations in four developing countries. *Pediatrics* 1981; 68:677-683
 39. Diop B, Collignon R, Gueye M, et al: Psychiatric symptomatology and diagnosis in a rural area of Senegal. *Psychopathologie Africaine* 1980; 16(1):5-20
 40. Giel R, Bishaw M, van Luijk JN: Behavior disorders in Ethiopian children. *Psychiatr Neurol Neurochir* 1969; 72:395-400
 41. Basher TA, Cadabald M: A Child Psychiatric Study on Sudane Arab Children. *Acta Psychiatr Scand (Suppl)* 1968; 200
 42. Olatawura MO, Odejide AO: Child psychiatric disorders in Ibadan. *Nigerian J Paediatrics* 1976; 3(1):9-14
 43. Egdel AG: Child psychiatric services in Uganda. *Psychopathologie Africaine* 1970; 6(1):71-81
 44. Racy J: Somatization in Saudi women: a therapeutic challenge. *Br J Psychiatry* 1980; 137:212-216
 45. Prince R: The changing picture of depressive syndromes in Africa: is it fact or diagnostic fashion? *Canadian J African Studies* 1968; 1:177-192
 46. Rwegellera GGC: Cultural aspects of depressive illness: clinical aspects and psychopathology. *Psychopathologie Africaine* 1981; 17(1/2/3):41-63
 47. Weiss MG, Kleinman A: Depression in cross-cultural perspective: developing a culturally informed model, in *Health and Cross-Cultural Psychology*. Edited by Dasen PR, Berry JW, Sartorius N. Newbury Park, Calif, Sage Publications, 1988
 48. Field MJ: *Search for Security: An Ethno-Psychiatric Study of Rural Ghana*. London, Faber and Faber, 1960
 49. Majodina MZ, Johnson FYA: Standardized assessment of depressive disorders in Ghana. *Br J Psychiatry* 1983; 143:442-446
 50. Paes M, Chkli T, Kionet J, et al: Clinical aspects of manic-depressive psychosis in Morocco. *Psychopathologie Africaine* 1981; 17(1/2/3):31-35
 51. Guelfi JD, Sirion M, Monier C, et al: A comparative study of depressive symptomatology on French and Maghrebians in-patients. *Psychopathologie Africaine* 1981; 17(1/2/3):171-189
 52. Hanck CH, Gutierrez AJ, Brieva RJA: Clinical aspects of depressive illness and culture: a comparative study in Spain/Senegal. *Psychopathologie Africaine* 1981; 17(1/2/3):73-78
 53. Ammar S, Douki S, Boucebi M, et al: Depression in Maghreb: clinical and psychopathological aspects. *Psychopathologie Africaine* 1981; 17(1/2/3):16-26
 54. Collomb H, Zwengelstein J: Depressive states in an African community, in *First Pan-African Psychiatric Conference, Abeokuta*, 1961. Edited by Lambo TA. Ibadan, Nigerian Government Printer, 1962
 55. Lambo TA: Neuropsychiatric observations in the Western region of Nigeria. *Br Med J* 1956; 2:1388-1394
 56. Jegede RO: Depression in Africans revisited: a critical review of the literature. *Afr J Med Sci* 1979; 8:125-132
 57. Gillis LS: Observations from South Africa, in *First Pan-African Psychiatric Conference, Abeokuta*, 1961. Edited by Lambo TA. Ibadan, Nigerian Government Printer, 1962
 58. Binitie AO: The clinical manifestations of depression in Africans. *Psychopathologie Africaine* 1981; 17(1/2/3):36-40
 59. Morakinyo O: Phobic states presenting as somatic complaints: syndromes in Nigeria. *Acta Psychiatr Scand* 1985; 71:356-365
 60. Makanjuola RO: Recurrent unipolar manic disorder in the Yoruba Nigerian: further evidence. *Br J Psychiatry* 1985; 147: 434-437
 61. Lamont AM, Blignault WJ: A study of male Bantu-admissions at Weskoppies during 1952. *S Afr Med J* 1953; 27:637-639
 62. Wig NN, Menon DK, Bedi H, et al: Expressed emotion and schizophrenia in North India, II: distribution of expressed emotion components among relatives of schizophrenic patients in Aarhus and Chandigarh. *Br J Psychiatry* 1987; 151:160-165
 63. Akindele MC, Odejide AO: Catatonic-schizophrenia in Ibadan. *Nigerian Med J* 1973; 4(4):256-258
 64. Okasha A, Lotaif F: Attempted suicide: an Egyptian investigation. *Acta Psychiatr Scand* 1979; 60:69-75
 65. Beall L: The dynamics of suicide: review of the literature 1897-1965. *Reflections: A Merck Sharpe and Dohme Publication for the Psychiatrist* 1969; 5(5):12-38
 66. Rwegellera GGC: Suicide rates in Lusaka, Zambia: preliminary observations. *Psychol Med* 1978; 8:423-432
 67. Odejide AO, Williams AO, Ohaeri JU, et al: The epidemiology of deliberate self-harm: the Ibadan experience. *Br J Psychiatry* 1986; 149:734-737
 68. *Community Response to Alcohol-Related Problems: A WHO Project Monograph*. Washington, DC, US Department of Health and Human Services, National Institute on Alcohol Abuse and Addiction, 1984
 69. Odejide AO, Olatawura MO: Alcohol use in a Nigerian rural community. *Afr J Psychiatry* 1977; 1(1):69-74
 70. El-Mahi T: The alcohol problem in the Sudan, in *Selected Essays of Tigani El-Mahi*. Edited by Safi A, Baasher T. Khartoum, Sudan, Khartoum University Press, 1981
 71. Atiyeh M: Arab hospitals in history. *King Faisal Specialist Hospital Med J* 1982; 2(2):121-126
 72. Gills LS: The Cape Town Psychiatric Service. *S Afr Med J* 1979; 56:970-973
 73. Levin A: Modern psychiatry in a general hospital. *S Afr Med J* 1978; 54:743-747
 74. Apartheid and mental health care: a preliminary review by the WHO Secretariat of the available information on mental health services in the Republic of South Africa. *Psychopathologie Africaine* 1978; 14(1):69-98

75. Psychiatry for Africa (editorial). *S Afr Med J* 1979; 55:149-150
76. Retief FP: The Medical University of South Africa after 5 years. *S Afr Med J* 1982; 62:841-845
77. Mankazana EM: A case for the traditional healer in South Africa. *S Afr Med J* 1979; 56:1003-1007
78. Dhadphale M, Shaikh SP: Psychiatric diagnosis of 236 admissions seen at Ndola, Zambia. *East Afr Med J* 1981; 58:65-71
79. Rwegellera GGC: The present state of psychiatry in Zambia and suggestions for future development. *Psychopathologie Africaine* 1980; 16(1):21-38
80. Collomb H: The history of psychiatry in French-speaking African countries. *Afr J Psychiatry* 1975; 1(2):87-116
81. Coulibay B, Koumare B, Coudray J: The need for psychiatric help in Mali: epidemiological facts from hospital work. *Psychopathologie Africaine* 1983; 19(3):261-286
82. Osouf P: Survey of mental health care in Niger. *Psychopathologie Africaine* 1980; 16(3):249-280
83. Gueye M, M'Bousson M: The evolution of therapeutic conceptions of depressive illness during 20 years in Fann Hospital, 1961-1968 to 1980. *Psychopathologie Africaine* 1981; 17(1/2/3):197-208
84. Odejide AO: Cross-cultural psychiatry: a myth or reality. *Compr Psychiatry* 1979; 20:103-109
85. Odejide AO, Ohaeri JU, Ikuesan BA: Electroconvulsive therapy in Nigeria. *Convulsive Therapy* 1987; 3(1):31-39
86. Olatawura MO: Psychotherapy for the Nigerian patient: some aspects of the problems involved. *Psychother Psychosom* 1975; 25:259-266
87. Warmann WA: The use of aversion therapy to treat kleptomania. *Psychopathologie Africaine* 1980; 16(1):77-82
88. Beigel A: New approaches to the delivery of mental health care in Africa. *Psychopathologie Africaine* 1981; 17(1/2/3):262-270
89. Murphy HBM: Alternatives to classical forms of psychiatric care. *Psychopathologie Africaine* 1981; 17(1/2/3):253-261
90. Boroffka A: Psychiatry in Nigeria today and tomorrow. *Nigerian Med J* 1970; 7:36-39
91. Collignon R: An example of community psychiatry in black Africa: the village system—elements for a dossier. *Psychopathologie Africaine* 1983; 19(3):287-328
92. WHO Expert Committee on Mental Health: Organization of Mental Health Services in Developing Countries: WHO Technical Report Series 564, 16th Report. Geneva, World Health Organization, 1975
93. Lewis A: Inaugural speech, in First Pan-African Psychiatric Conference, Abeokuta, 1961. Edited by Lambo TA. Ibadan, Nigerian Government Printer, 1962

A Prospective Analysis of 24 Episodes of Neuroleptic Malignant Syndrome

Patricia Rosebush, M.Sc.N., M.D., F.R.C.P.(C), and Thomas Stewart, M.D.

The authors prospectively studied 24 consecutive cases of neuroleptic malignant syndrome occurring in 20 patients in a general hospital over a 6-year period. They present detailed data concerning the clinical setting in which neuroleptic malignant syndrome occurs, the associated clinical and laboratory features, the favorable outcome that can be achieved with vigorous supportive therapy, and the factors that might help predict whether patients with neuroleptic malignant syndrome will subsequently be able to tolerate the reintroduction of neuroleptic medication.

(Am J Psychiatry 1989; 146:717-725)

Over the past 20 years it has become evident that a minority of patients treated with neuroleptic medication develop a fulminant and potentially life-threatening illness characterized by hyperthermia, delirium, and severe extrapyramidal symptoms. Neuroleptic malignant syndrome, as this condition has come to be known, was first described by Delay and Deniker in 1968 (1). Since that time the literature on the syndrome has been comprised largely of case reports, and in the past several years there has been a proliferation of reviews of these extant case studies (2-9). Insufficient information is provided for many cases, and there is considerable variation in the diagnostic criteria used both by authors of the primary data studies and by reviewers of the literature. These problems have recently been reviewed by Levinson and Simpson (5).

Presented in part at the 141st annual meeting of the American Psychiatric Association, Montreal, May 7-12, 1988. Received June 6, 1988; revision received Nov. 30, 1988; accepted Dec. 8, 1988. From the Department of Psychiatry, Beth Israel Hospital, Boston. Address reprint requests to Dr. Rosebush, Department of Psychiatry, McMaster University Medical Centre, 1200 Main St. West, Hamilton, Ont. L8N 3Z5, Canada.

Copyright © 1989 American Psychiatric Association.

The largest series reported in the English language literature to date has included nine patients (10); however, the information provided was incomplete, and it is unclear whether the authors studied these patients prospectively. For the most part, the study of neuroleptic malignant syndrome has involved either analysis of data obtained by different clinicians or retrospective chart review.

We have had the opportunity to prospectively study 24 episodes of neuroleptic malignant syndrome in detail. To our knowledge, the series constitutes the largest reported in the world literature.

METHOD

Patients were included in this series if fever, rigidity, and mental status changes developed suddenly and concurrently during neuroleptic medication use and if no other medical condition that might fully account for the same clinical picture could be identified. We studied 24 episodes of neuroleptic malignant syndrome occurring in 20 patients over a period of 6 years (from 1981 to 1987). Symptoms of neuroleptic malignant syndrome developed in 14 patients during psychiatric hospitalization; in three residing in nursing homes; in two patients hospitalized for treatment of other medical illnesses; and in one living at home. Psychiatric diagnoses were made before the development of neuroleptic malignant syndrome by psychiatrists at university-affiliated hospitals, and they met *DSM-III* criteria. Neuroleptic dosage in each case was converted to chlorpromazine equivalents, as outlined by Davis (11). Two patients had one repeat episode (cases 1, 2, 10, and 11), and one patient had two repeat episodes (cases 13, 14, and 15). All patients had extensive laboratory investigations. Chest X-rays as well as cultures of blood, urine, and sputum were done in all cases. Lumbar puncture with CSF cultures was performed

TABLE 1. Treatment and Illness Characteristics of 24 Patients With Neuroleptic Malignant Syndrome

Case	Sex	Age (years)	Diagnosis	Neuroleptic Dose Change ^a	Treatment	Duration of Syndrome (days)
1	F	25	Affective disorder	? to 1200	Supportive	9
2	F	25	Affective disorder	200 to 1000	Supportive	11
3	M	50	Affective disorder	0 to 300	Supportive, dantrolene, bromocriptine	10
4	F	45	Affective disorder	300 to 300	Supportive, bromocriptine	8
5	F	40	Affective disorder	0 to 3500	Supportive, dantrolene	13
6	F	41	Brief reactive psychosis	0 to 750	Supportive, dantrolene	12
7	F	39	Affective disorder	400 to 3400	Supportive	5
8	F	59	Affective disorder	0 to 600	Supportive	5
9	F	53	Affective disorder	0 to 1500	Supportive	10
10	M	50	Schizophrenia	0 to 1250	Supportive	5
11	M	50	Schizophrenia	0 to 750	Supportive	4
12	M	31	Brief reactive psychosis	0 to 1000	Supportive, bromocriptine	8
13	F	69	Affective disorder	500 to 500	Supportive	5
14	F	69	Affective disorder	500 to 500	Supportive	4
15	F	69	Affective disorder	500 to 500	Supportive	4
16	F	17	Atypical psychosis	200 to 520	Supportive, dantrolene, bromocriptine	6
17	M	24	Affective disorder	0 to 480	Supportive	4
18	M	19	Affective disorder	0 to 750	Supportive	6
19	F	57	Atypical psychosis	750 to 750	Supportive	7
20	F	66	Affective disorder	300 to 300	Supportive, bromocriptine	8
21	M	35	Affective disorder	600 to 240	Supportive	9
22	M	20	Schizophreniform psychosis	80 to 850	Supportive	6
23	F	45	Affective disorder	0 to 2250	Supportive, dantrolene, bromocriptine	28
24	F	92	Affective disorder	? to 100	Supportive	11

^a Within 1 week before the onset of neuroleptic malignant syndrome; measured in milligrams of chlorpromazine equivalents.

during 19 of the 24 episodes and EEG studies were done in eight cases.

Patients were considered to be dehydrated if from the time of admission to the time of discharge at least two of the following were present: 1) a 10% or greater decrease in hematocrit without intervening hemorrhage, 2) a 40% or greater decrease in serum levels of BUN, and 3) a 50% or greater decrease in serum creatinine concentration. The values on recovery were normal, and therefore the higher values at admission were taken as evidence of hemoconcentration. Lithium toxicity was defined as a serum blood level greater than 1.5 mmol/liter.

RESULTS

Clinical Setting

Neuroleptic malignant syndrome developed in 13 women, with a mean \pm SD age of 49.8 ± 19.5 years (range=17–92 years), and in seven men, with a mean age of 32.7 ± 13 years (range=19–50 years). Affective disorder was the primary psychiatric diagnosis in 14 of the 20 patients. The remaining diagnoses included brief reactive psychosis (N=2), atypical psychosis (N=2), schizophrenia (N=1), and schizophreniform psychosis (N=1). Before 20 of the 24 episodes, patients were acutely psychotic: 18 were agitated, while two

were withdrawn and quiet. In the remaining four cases, which developed outside a hospital setting, there was not enough evidence to determine whether or not the patients were psychotic or agitated beforehand. No physical restraints were used with any patient. Every episode of neuroleptic malignant syndrome that developed in patients hospitalized for psychiatric illness (N=16) occurred within the first month of admission, and all but two cases developed within the first 2 weeks. Twelve (50%) of the episodes occurred in summer (June, July, August) while only one episode occurred during the winter months of December to February. Information about whether or not patients were in air-conditioned surroundings at the time they developed neuroleptic malignant syndrome was present for 11 of these 12 episodes. In five instances there was air conditioning and in six instances there was not.

Drugs

Twelve (60%) of the 20 patients had a history of earlier neuroleptic exposure, but none had a previously documented episode of neuroleptic malignant syndrome. Characteristics of patients and neuroleptic use before the 24 episodes are shown in table 1. Six different neuroleptic drugs were prescribed. Haloperidol was administered either alone or with another neuroleptic in 14 of the 24 episodes. The daily neuroleptic dose in chlorpromazine equivalents ranged from 80 to

3500 mg and was 1000 mg or greater in eight cases. In five of nine cases patients who developed neuroleptic malignant syndrome while taking the chlorpromazine equivalent of 500 mg/day or less were over the age of 65. The episode precipitated by the chlorpromazine equivalent of 50 mg (case 11) occurred when a patient was rechallenged within 24 hours after resolution of a previous episode. In 15 (65%) of 22 cases for which we have sufficient data, neuroleptics had been given for the first time (N=4), reintroduced after a drug-free interval (N=7), or increased in dose (N=4) within the previous 7 days. Five patients developed neuroleptic malignant syndrome while on regimens of stable or reduced neuroleptic dosages, and in four of the five, severe dehydration clearly preceded the onset of the syndrome (cases 4, 19, 20, and 24). The fifth patient (case 13) was an elderly woman from a nursing home who developed neuroleptic malignant syndrome while receiving a stable dose of neuroleptic 5 days after an increase in lithium. She then had two repeat episodes when neuroleptic reintroduction was attempted.

Lithium was being used at the time neuroleptic malignant syndrome developed in 14 (58%) of the 24 episodes, and toxic levels were measured in four. In two patients the lithium toxicity clearly followed the onset of neuroleptic malignant syndrome and appeared to be secondary either to myoglobinuric renal failure or to the dehydration that occurred after the neuroleptic malignant syndrome episode began. In two other cases with severe dehydration, it was impossible to discern the exact sequence of dehydration, lithium toxicity, and neuroleptic malignant syndrome. Non-neuroleptic medications with anticholinergic properties were being used concurrently with the neuroleptics in 16 (67%) of the 24 cases, and benzodiazepines were being prescribed in seven (29%).

Concurrent Medical Illness

No additional active medical illness could be identified in 15 (63%) of the 24 cases. In three of the nine remaining episodes (cases 4, 10, and 22) the patient had either respiratory or urinary tract infection. In case 4, the patient also had adult-onset diabetes, with profound dehydration and lithium toxicity. A fourth patient (case 3) developed neuroleptic malignant syndrome while abusing both lidocaine and alcohol. Case 6 involved a patient with gastroenteritis and dehydration following a small bowel resection for Crohn's disease. She became acutely agitated and psychotic. Within 24 hours of receiving neuroleptics, she developed neuroleptic malignant syndrome. In case 12, neuroleptic malignant syndrome occurred in a young man hospitalized with newly diagnosed acquired immune deficiency syndrome (AIDS) and a pneumocystis carinii infection. Shortly after learning of his diagnosis, he became agitated and paranoid. He was given neuroleptics and within 24 hours developed the full manifestations of the syndrome. Neuroleptic malignant syndrome developed in a 66-year-old woman (case 20),

receiving a stable dose of neuroleptic and lithium, when she became markedly dehydrated and lithium toxic secondary to a gastrointestinal hemorrhage.

In case 21, neuroleptic malignant syndrome occurred in a man who developed hyperosmolar nonketotic syndrome while being treated in a psychiatric hospital for a psychotic illness. While being transferred to a general hospital for treatment of his profound dehydration and hyperglycemia, he developed neuroleptic malignant syndrome, which was heralded by a temperature rise to 108 °F. Case 23 involved a patient whose long-standing medications of lithium, perphenazine, and amitriptyline were abruptly discontinued, whereupon she became acutely agitated and psychotic. Haloperidol was administered, and within 24 hours she developed neuroleptic malignant syndrome. In addition to these acute medical problems, nine patients (45%) had the following underlying conditions: seizure disorder, currently stable (cases 10, 11, and 19); chronic organic brain syndrome (cases 16, 20, and 24); previous cerebral vascular accident (case 8); cardiac disease, currently stable (cases 13, 14, 15, and 24); and chronic obstructive pulmonary disease (case 9).

Clinical Features of the Neuroleptic Malignant Syndrome

All patients (summarized in table 2) were profoundly ill and prostrate in bed. Delirium was present in all cases. Skin was warm and flushed, and all patients were diaphoretic. All patients had fever (mean \pm SD temperature = 103 ± 1.9 °F), tachycardia (mean heart rate = 136 ± 19.5 beats per minute), and tachypnea (respiratory rate = 34 ± 9.8 breaths per minute). Temperature was highest within the first 48 hours in 88% of the cases. Blood pressure was persistently high in 10 cases (44%), labile in eight cases (33%), low in two cases (8%), both of which involved marked dehydration, and normal in the other four. Muscular rigidity of all limbs was present in 23 (96%) of 24 cases, although it was best described as mild in three cases (cases 2, 3, and 5). Coarse tremulousness of the trunk and extremities was observed in 22 (92%) of 24 cases, and 14 (59%) involved a new movement disorder characterized by either dystonic posturing or choreiform movements of the extremities. Periods of muteness or hypophonia occurred within 48 hours in 23 (96%) of 24 cases. Incontinence developed in 13 (55%) of 24 cases, and a new macular papular rash on the trunk and extremities was noted in seven cases (30%).

A striking, frightened facial expression was observed in all cases. As 11 patients were later able to describe, this was accompanied by a wish to speak but an inability to do so. This inability to speak and a sense of impending doom had produced overwhelming anxiety. Two patients commented that throughout the episode they had been tormented by hallucinations to which they were unable to give voice.

TABLE 2. Clinical and Biochemical Characteristics of Patients With Neuroleptic Malignant Syndrome

Feature	Patients		
	Total	N	%
Clinical			
Fever	24	24	100
Tachycardia	24	24	100
Delirium	24	24	100
Diaphoresis	24	24	100
Rigidity	24	23	96
Muteness	24	23	96
Tremulousness	24	22	92
Movement disorder	24	14	58
Incontinence	24	13	54
Hypertension	24	10	42
Labile blood pressure	24	8	33
Dyspnea	24	7	29
Rash	24	7	29
Biochemical			
Blood			
Dehydration ^a	24	22	92
High creatinine phosphokinase level	23	21	91
High LDH level	22	20	91
Low iron level	20	19	95
High SGOT level	23	19	83
High SGPT level	22	13	59
Leukocytosis	24	18	75
Thrombocytosis	16	9	56
Low calcium level	24	13	54
Low magnesium level	16	10	63
High alkaline phosphatase level	24	5	21
Urine			
Proteinuria	23	21	91
Myoglobinuria	24	16	67
CSF protein	19	7	37
Diffuse slowing on EEG	7	7	100

^a See definition in text.

Laboratory Features

Dehydration. Dehydration was present in 22 (92%) of 24 cases at the time of presentation with neuroleptic malignant syndrome. In addition to meeting the criteria for dehydration outlined in the Methods section, six cases (25%) involved hypernatremia, with a serum sodium level of more than 150 meq/liter.

Muscle and liver enzymes. Creatinine phosphokinase was increased above the normal limit (0–200 IU/liter) in all 21 cases for which serial values were available. In one episode, levels were not determined and in two, values were determined only on day 1. Isoenzymatic analysis showed 99%–100% muscle fraction in all cases. Serum creatinine phosphokinase level was greater than 10,000 IU/liter in seven cases and greater than 1000 IU/liter in 18. Levels of LDH, SGOT, and SGPT all tended to be elevated but less dramatically than creatinine phosphokinase. In the 22 cases in which LDH was determined, only three involved values above 1000 IU/liter (normal=0–200 IU/liter), and none involved values greater than 2000 IU/liter. When cases with daily creatinine phosphokinase and LDH

levels were examined, peak levels occurred on days 2 and 3 in 64%, on days 4 to 7 in 29%, and on day 1 in only one instance (7%). SGOT was measured in 23 cases and was found to be elevated in 19 (83%), but in no instance was it greater than 700 IU/liter (normal=0–40 IU/liter). Similarly, SGPT, measured in 22 episodes, was elevated in 14 (64%) but was never more than 500 IU/liter (normal=0–40 IU/liter). Alkaline phosphatase was mildly elevated in five cases (21%), and bilirubin was normal in all cases.

Blood cell counts. White blood cell count was elevated in 18 cases (75%). In all cases in which the white blood cell count was greater than 20,000/mm³, lithium was being used concurrently. No eosinophilia was found. Platelet count was determined during 16 episodes and was above normal (150,000–440,000/mm³) in nine (56%).

Calcium and magnesium. Serum calcium values were determined at least once in all patients within the first week. Hypocalcemia (mean±SD serum calcium value=8.4±0.16 mg/dl), when corrected to an albumin level of 4.0 g/dl, was found in 13 cases (54%). Ionized calcium levels were not determined. Hypophosphatemia was noted in six cases, including two of those with hypocalcemia. Only one instance of hyperphosphatemia was seen. Serum magnesium was determined in 16 cases and was found to be low in 10 (65%), with a range of 1.5 to 1.9 mg/dl.

Serum iron. Serum iron levels were determined between 7:00 a.m. and 9:00 a.m. in 19 cases, and 18 (95%) involved values that fell below the normal range (52–180 mg/dl). In 13 cases, serum iron was below 40 mg/dl, and in seven, serum iron was 20 mg/dl or less. Levels were determined three or more times during 14 episodes. In all but one case, the lowest serum iron was recorded within 7 days of the onset of symptoms. The patient with a gastrointestinal hemorrhage was not included in this analysis.

Urinalysis. Proteinuria was present in 91% of the cases. In 16 cases (67%) there was evidence of myoglobinuria, and hemegranular casts were detected in seven.

Spinal fluid analysis. Cell counts and glucose were normal in all 19 cases in which CSF was examined. CSF protein was within the normal range in 12 cases (63%) and was elevated in seven (37%).

EEG. EEG recordings showed diffuse slowing without focal abnormality, consistent with a metabolic encephalopathy, in seven of the eight cases that were studied. In one instance the EEG was uninterpretable secondary to artifact caused by tremulousness.

COMPLICATIONS, TREATMENT, AND OUTCOME

Neuroleptics were discontinued, and all patients received intravenous fluid as well as antipyretic agents. Sixteen patients received antibiotics, although only five had identified infectious processes. Of 14 patients in which lithium was being used at the time neuroleptic

malignant syndrome symptoms developed, seven continued to have measurable levels of lithium throughout the course of their illness. Dantrolene and bromocriptine, either alone or together, were used in eight cases. In five cases, temperature and creatinine phosphokinase had begun to fall just before the drug was started. Mean \pm SD duration of the illness was 9.3 ± 2.4 days for those who received bromocriptine or dantrolene or both and 6.0 ± 3.0 days for those who did not. In a single case treated with both drugs within 48 hours of the onset of the syndrome, neuroleptic malignant syndrome persisted for 28 days; this case was a statistical outlier, as defined by Grubbs (12), and was not included in the calculation of the mean duration for the drug-treated group. Another patient (case 5), whose muscle biopsy later showed abnormal contractility in response to caffeine and halothane, clearly had no response to the use of dantrolene.

Fourteen patients continued to have extrapyramidal symptoms or mild abnormalities of vital signs and muscle enzymes at the time of discharge. These abnormalities could occur even after their conditions had normalized. In none of the 14 patients were the fluctuations related to efforts to reintroduce neuroleptics.

There were no deaths in this series. Prerenal azotemia developed in 16 cases (67%) and renal failure in seven (30%), two of which required hemodialysis. In five cases (21%) respiratory distress necessitated intubation. All but one of the patients in this series returned to the institution or residence from which they had been referred. The lone exception was the patient with AIDS, who was discharged to a nursing home with a persistent organic brain syndrome. Three patients continued to have parkinsonian symptoms until the time they were lost to follow-up 1, 3, and 5 months later. One patient complained of persistent muscle weakness for months after her discharge. Another patient with mild cognitive impairment before the episode had a clear and persistent worsening of her dementia for 3 months after resolution of the neuroleptic malignant syndrome (case 24).

Marked anomia was evident in two patients (cases 9 and 23) in the early recovery period and cleared over a matter of weeks in both. Another patient with a long history of exposure to neuroleptics developed a severe tardive dyskinesia for the first time when low-dose neuroleptics were reintroduced 6 months later (case 8).

Neuroleptics were reintroduced to 15 patients. Thirteen (87%) were eventually able to take this medication again. The most important variable affecting the ability of patients to tolerate reintroduction was the time that had elapsed after the resolution of neuroleptic malignant syndrome. Neuroleptics were safely reintroduced if 2 weeks or more had passed since recovery from the episode (13). The choice of a neuroleptic lower in potency and dosage than that which precipitated the initial neuroleptic malignant syndrome episode was not significantly related to successful outcome. Two patients had a reemergence of some signs of neuroleptic malignant syndrome (fever, diaphoresis, rigidity)

when lithium, not neuroleptic, treatment was restarted.

DISCUSSION

Our data point to a number of factors that appear to predispose subjects to the development of neuroleptic malignant syndrome. Neuroleptics were either newly introduced or increased in dosage in 15 (65%) of the 22 cases for which we have full data. Increase in dosage is clearly not a sufficient explanation for the development of this syndrome, given the frequency of such an intervention in the psychiatric population at large and the low prevalence of neuroleptic malignant syndrome. Nevertheless, it may be a risk factor for those individuals who are otherwise vulnerable. While early reports suggested that there is no relationship between absolute neuroleptic dosage and the occurrence of neuroleptic malignant syndrome, in our series, 15 of the 19 nongeriatric cases who developed neuroleptic malignant syndrome for the first time were receiving dosages in excess of 500 mg of chlorpromazine equivalent per day. There is accumulating evidence (14, 15) that other types of neuroleptic toxicity increase with dosage, and it would appear that neuroleptic malignant syndrome joins the growing list of side effects that are dose related. It is prudent, whenever clinically possible, to treat extrapyramidal side effects by lowering the dosage of medication.

One of the most striking findings in our series is that only one of the 20 patients who developed neuroleptic malignant syndrome had a diagnosis of schizophrenia, while 14 had affective disorders. Indeed, chart review revealed that even the one patient who had been diagnosed as schizophrenic was on a regimen of lithium and was severely agitated before developing neuroleptic malignant syndrome; this raises the question of whether there was a major affective component to his illness. This low ratio of schizophrenia to affective disorder is unlikely to be simply selection bias, as the Massachusetts Mental Health Center, Sunnybrook Medical Centre, and the hospitals from which patients were referred to Beth Israel Hospital for treatment are all institutions that see a high proportion of schizophrenic patients. Other investigators have suggested that affectively disordered patients may have a greater predisposition to certain neuroleptic side effects such as tardive dyskinesia (16–18) and neuroleptic malignant syndrome (19). A preponderance of affective disorder in patients who develop neuroleptic malignant syndrome may reflect a state-dependent vulnerability such as has been proposed for lithium toxicity (20) and neuroleptic-induced dyskinesias (21). Virtually all patients for whom data are available were acutely agitated before developing neuroleptic malignant syndrome. It is possible that agitation and restlessness represented undiagnosed akathisia, which might create a state-dependent predisposition to neuroleptic malignant syndrome. Since 12 (86%) of the 14 patients with

affective disorders were taking antidepressants or lithium or both, the increased vulnerability to neuroleptic malignant syndrome may be related to the concurrent use of these medications.

Forty-two percent of the patients in this series suffered from another form of brain pathology or vulnerability in addition to psychiatric illness. This includes the six patients with underlying seizure disorders, chronic organic brain syndromes, or cerebral vascular accidents (cases 8, 10, 11, 16, 19, 20, and 24), the individual with AIDS (case 12), and two patients with either drug withdrawal or intoxication (cases 3 and 23). This finding suggests that any CNS compromise increases the risk of developing neuroleptic malignant syndrome.

Most patients were dehydrated. While in several cases the history quite clearly indicated that dehydration predated the onset of neuroleptic malignant syndrome, in most instances it was difficult to determine whether the dehydration that was present on admission to the hospital preceded or followed the onset of the syndrome. This issue is particularly difficult to sort out since fever, marked diaphoresis (22), and decreased fluid intake after the onset of the syndrome can themselves lead to dehydration. Whether a primary or a secondary feature of the illness, dehydration may contribute to the development of fulminant neuroleptic malignant syndrome by increasing the effective concentration of neuroleptic in the extracellular fluids. This is certainly suggested by the fact that in four cases, patients developed neuroleptic malignant syndrome while on stable doses of neuroleptics when they became severely dehydrated and by the one case in which neuroleptic malignant syndrome occurred despite a reduction in neuroleptic dose when profound dehydration was present. Dehydration alone would not cause diaphoresis, high creatinine phosphokinase levels, mutism, and labile or elevated blood pressure.

DIFFERENTIAL DIAGNOSIS

While all patients showed a striking stereotypical clinical picture, there are several other conditions that must be considered in the differential diagnosis of neuroleptic malignant syndrome.

Other Conditions

Infection plus neuroleptic side effects. One of the more difficult problems in the differential diagnosis of neuroleptic malignant syndrome is presented by the patient who develops infection while taking neuroleptics. Over the 6-year course of this study, we saw many patients with neuroleptic-induced side effects plus infection but diagnosed neuroleptic malignant syndrome in only five. These five patients were clearly distinguished from the others by the fulminant onset and severity of extrapyramidal signs and symptoms, as well as by the presence of delirium, marked akinesia, mut-

ism, and rhabdomyolysis. Neuroleptic-treated patient with a CNS infection can present with fever, delirium and even rhabdomyolysis secondary to seizures, falls or coma. We excluded all cases with CNS infection from our series and recommend that a lumbar puncture be performed whenever the diagnosis of neuroleptic malignant syndrome is being considered. Clinician should not be reluctant to make a diagnosis of neuroleptic malignant syndrome in the presence of a non-CNS infection, as they may often coexist. Infection may predispose subjects to neuroleptic malignant syndrome by producing dehydration. Conversely, neuroleptic malignant syndrome may create a setting for infection as a result of respiratory compromise, immobility, and urinary catheterization.

Other drug toxicities. Several features of neuroleptic malignant syndrome are seen in anticholinergic toxicity (23). Fever, tachycardia, delirium, and a history of psychotropic medication use are found in both conditions. However, anticholinergic toxicity is characterized by an absence of sweating instead of diaphoresis, hypotension versus lability or an increase in blood pressure, urinary retention rather than incontinence and agitation as opposed to the muteness, rigidity, and akinesia typical of patients with neuroleptic malignant syndrome. Similarly, leukocytosis, elevated muscle enzymes, and myoglobinuria have not been described in anticholinergic toxicity. It is nevertheless still possible that a deficiency in cholinergic transmission may contribute to some of the clinical features of neuroleptic malignant syndrome.

Over half of the patients in this series were taking lithium, and in two cases the initiation of lithium therapy alone led to a reappearance of neuroleptic malignant syndrome. This raises the question of the relationship between lithium and neuroleptic malignant syndrome. Lithium toxicity is not associated with fever and typically produces weakness, lethargy, cerebellar dysfunction, fasciculations, myoclonus, and seizure (24, 25)—a clinical picture quite easily distinguishable from neuroleptic malignant syndrome. Lithium may predispose to neuroleptic malignant syndrome by rendering the brain more vulnerable to neuroleptic side effects (26, 27). In addition, lithium can cause diabetes insipidus and dehydration, which may in turn result in an effective increase in neuroleptic concentration.

The ability of lithium alone to produce extrapyramidal side effects appears to be rare (28–30). However the findings of reduced dopamine synthesis in rats after chronic lithium therapy (31), worsening of preexisting extrapyramidal symptoms during lithium use (32), and the report of akathisia in a patient taking lithium alone (33) suggest that lithium might affect the dopaminergic system in a way similar to neuroleptics. Another report of lithium toxicity described rhabdomyolysis and elevated levels of creatine phosphokinase, although it did not specify whether the patient had also received neuroleptics (34). Lithium toxicity has been associated with rigidity, although in most instances neuroleptics are being used concurrently.

(35–37) or there is failure to report their use (38–41). Patients with evidence of both neuroleptic malignant syndrome and lithium toxicity have been described (42).

Catatonia. It is important to distinguish psychogenic catatonia from neuroleptic malignant syndrome. Patients with this disorder have varying combinations of catalepsy, mutism, immobility, negativism, echolalia, echopraxia, stereotypy, grimacing, and posturing (43). Hyperthermia, autonomic instability, and elevation of muscle enzymes are rarely present. Patients with psychogenic catatonia usually improve, rather than worsen, when given neuroleptics. No one in our series had a history of catatonia, and all patients improved when neuroleptics were discontinued. There are several reports from the preneuroleptic era of a syndrome with clinical features remarkably similar to those seen with neuroleptic malignant syndrome (44–48). This earlier syndrome, which has been termed lethal catatonia (49), consisted of intense psychomotor activity with fever, diaphoresis, tachycardia, labile blood pressure, altered consciousness, and mutism, eventually giving way to stupor and exhaustion. Affectively disordered patients may be overrepresented in this condition (50). The relationship between lethal catatonia and neuroleptic malignant syndrome is presently not clear, but it is possible that the two disorders share the same underlying pathophysiology.

Malignant hyperthermia. Many observers have commented on the similarity between neuroleptic malignant syndrome and malignant hyperthermia. Both are characterized by fever, delirium, a hypermetabolic state of skeletal muscle, and rhabdomyolysis. The possibility of an etiological connection between the two syndromes has been strengthened by reports of abnormal muscle biopsies in patients who develop neuroleptic malignant syndrome (51) and the apparent success of dantrolene as a treatment agent in both conditions (52–56). In our series, only one patient had a muscle biopsy, which showed abnormal contractility to caffeine and halothane. Another patient in our series had a niece with malignant hyperthermia. There are important differences between malignant hyperthermia (57, 58) and neuroleptic malignant syndrome. The precipitating stimuli are different; malignant hyperthermia occurs in response to halogenated inhalational anesthetic agents and depolarizing muscle relaxants such as succinylcholine. Neuroleptics have actually been used in the treatment of malignant hyperthermia (57), and there are numerous reports of patients with neuroleptic malignant syndrome who have gone on to receive anesthesia without incident (59). To date, there has not been a case report of someone who has suffered from both syndromes. That is not to say, however, that they cannot coexist.

Heat stroke. The occurrence of many episodes of neuroleptic malignant syndrome during the summer months raises the question of heat stroke. There are certain features that allow one to distinguish between neuroleptic malignant syndrome and heat stroke (60,

61). Patients with heat stroke are typically not diaphoretic or rigid, and blood pressure is usually low. The biochemical profile is that of metabolic acidosis secondary to shock and hypoxemia. The etiology of heat stroke in psychiatric patients may be related to the inhibition of sweating secondary to anticholinergic medications.

The fact that 12 of our cases occurred during the summer months while only one occurred from December to February is consistent with the previous observation that high ambient temperatures may be a predisposing factor to neuroleptic malignant syndrome (62). However, no firm conclusion can be drawn given that half of the “summer” episodes developed in air-conditioned environments.

Status epilepticus. This condition may mimic neuroleptic malignant syndrome. One of us (P.R.) has seen a case of status petit mal seizures that was remarkably similar to neuroleptic malignant syndrome. Marked rigidity, full body tremor, muteness, and a frightened stare were all present in this patient, who was taking a dopamine-blocking agent. Fever, tachycardia, and blood pressure lability were also present, although to a lesser extent. The EEG was diagnostic, showing a focal spike and wave pattern rather than diffuse slowing. It is also noteworthy that despite the severe rigidity, creatinine phosphokinase levels were only marginally elevated, other muscle enzymes were normal, no leukocytosis was present, and the patient was not diaphoretic. EEG studies should be done when possible in all cases of suspected neuroleptic malignant syndrome. The two patients (three episodes) in our series with a history of epilepsy had EEGs compatible with a diffuse encephalopathy, not seizures.

Drug allergy. Rash has not been previously reported in neuroleptic malignant syndrome. Its occurrence in seven patients suggests that drug allergy may play a role in the illness in some cases; however, the absence of eosinophilia and lack of any consistent relationship between the initiation of neuroleptics and the onset of a rash would suggest that this is unlikely.

Laboratory Abnormalities

One of the most striking findings in this series was the consistent and dramatic fall in serum iron concentration. This finding, which to our knowledge has not been previously reported, may in fact be an important marker for the illness. Hypoferremia is known to occur in febrile infectious conditions in response to the production of endogenous pyrogen by leukocytes (63). However, two episodes (cases 2 and 6) in which infection and fever were present before the development of neuroleptic malignant syndrome and in which iron levels were measured before and during neuroleptic malignant syndrome suggest that infection or fever alone may not fully account for the precipitous drops. In both instances, serum iron level had dropped to below normal before neuroleptic malignant syndrome but then showed a further reduction of greater than 50%

with the onset of the syndrome. Hypoferremia has been reported in strenuous exercise (64) and myocardial infarction (65–68), suggesting that muscle injury may be responsible. Whatever the underlying etiology, reductions in serum iron may contribute to the pathophysiology of the disorder, as iron has been implicated in striatal dopamine receptor function (69–72).

It is commonly believed that neuroleptic malignant syndrome is associated with hepatic dysfunction. In our series, we did not find good evidence to substantiate this. Alkaline phosphatase and bilirubin were normal or only minimally elevated (in the case of the former) in every case. Other liver function indices such as LDH, SGOT, and SGPT were elevated, but these enzymes are also found in muscle, and there seems little need to invoke a hepatic etiology.

The cause of the hypocalcemia is not clear. Values were corrected for albumin loss. Calcium levels may fall during rhabdomyolysis secondary to sequestration in muscle (73). All patients with creatinine phosphokinase levels above 10,000 IU/liter were hypocalcemic. Typically, however, phosphorus is elevated in these instances, and only one patient in this series had hyperphosphatemia. Renal failure can cause hypocalcemia in the oliguric phase, but there was no consistent relationship between the finding of low calcium and the presence of renal failure. While hypomagnesemia can lead to hypocalcemia, the levels seen during the episodes of neuroleptic malignant syndrome in this series were not low enough (74). The elevated platelet count most likely represents a reactive thrombocytosis which is seen in a number of acute conditions including trauma, infection, and inflammatory disease (75).

Treatment

A mortality rate of 20%–30% for neuroleptic malignant syndrome has been cited since the early reports in the literature. In this series, there were no fatalities and there were few sequelae. Clearly, with good supportive care in hospital, the illness need not be fatal and in fact has a good prognosis. Perhaps the high fatality rate reported to date will decrease as familiarity with the syndrome increases and an early diagnosis is made. It did not seem that the zero fatality rate could be attributed to an exclusion of severe cases. In fact, all patients in this series were profoundly ill and had a mean duration of illness identical to that described in the literature. Beyond what can be achieved with supportive care and discontinuation of neuroleptics, this series does not support the usefulness of bromocriptine and dantrolene. The natural course of the illness is improvement, although there can be fluctuations in vital signs and enzyme levels for a considerable length of time. As this series suggests, many patients experience profound anxiety during the illness secondary to untreated psychosis and feelings of impending doom. Benzodiazepines should be seriously considered during the treatment of neuroleptic malignant syndrome both for the patient's comfort and to decrease the hyperad-

renergic state, which may contribute to the pathophysiology of the disorder (76).

REFERENCES

1. Delay S, Deniker P: Drug-induced extra-pyramidal syndromes, in *Handbook of Clinical Neurology: Diseases of the Basal Ganglia*. Edited by Vinken PS, Bruyn GW. Amsterdam, North-Holland, 1968
2. Caroff SN: The neuroleptic malignant syndrome. *J Clin Psychiatry* 1980; 41:79–82
3. Levenson JL: Neuroleptic malignant syndrome. *Am J Psychiatry* 1985; 142:1137–1145
4. Guze BH, Baxter LR: Neuroleptic malignant syndrome. *N Engl J Med* 1985; 313:163–166
5. Levinson DF, Simpson GM: Neuroleptic-induced extra-pyramidal symptoms with fever. *Arch Gen Psychiatry* 1986; 43:839–848
6. Shalev A, Munitz H: The neuroleptic malignant syndrome: agent and host interaction. *Acta Psychiatr Scand* 1986; 73:337–347
7. Pearlman CA: Neuroleptic malignant syndrome: a review of the literature. *J Clin Psychopharmacol* 1986; 6:257–272
8. Addonizio G, Susman VL, Roth SD: Neuroleptic malignant syndrome: review and analysis of 115 cases. *Biol Psychiatry* 1987; 22:1004–1020
9. Kellam AM: The neuroleptic malignant syndrome, so-called. *Br J Psychiatry* 1987; 150:752–759
10. Harsch HH: Neuroleptic malignant syndrome: physiological and laboratory findings in a series of nine cases. *J Clin Psychiatry* 1987; 44:328–333
11. Davis JM: Comparative doses and costs of antipsychotic medication. *Arch Gen Psychiatry* 1976; 33:858–861
12. Grubbs FE: Procedures for detecting outlying observations in samples. *Technometrics* 1969; 11:1–22
13. Rosebush P, Stewart T: Reintroduction of neuroleptics following neuroleptic malignant syndrome. *J Clin Psychiatry* (in press)
14. Neborsky R, Janowsky D, Munson E, et al: Rapid treatment of acute psychotic symptoms with high and low dose haloperidol. *Arch Gen Psychiatry* 1981; 38:195–199
15. Marder SR, Van Putten T, Mintz J, et al: Low and conventional dose maintenance therapy with fluphenazine decanoate. *Arch Gen Psychiatry* 1987; 44:518–521
16. Gelenberg A: Patients with affective illness: are they more prone to develop TD? *Massachusetts General Hospital Newsletter* 1984; 7(2):6
17. Kane JM, Woerner M, Weinhold P, et al: Incidence and severity of tardive dyskinesia in affective illness, in *Scientific Proceedings of the 136th annual meeting of the American Psychiatric Association*. Washington, DC, APA, 1983
18. Yassa R, Ghadirian AM, Schwartz G: The prevalence of tardive dyskinesia in affective disorder patients. *J Clin Psychiatry* 1983; 44:410–412
19. Keck PE Jr, Pope HG Jr, McElroy SL: Frequency and presentation of neuroleptic malignant syndrome: a prospective study. *Am J Psychiatry* 1987; 144:1344–1346
20. West AP, Meltzer HY: Paradoxical lithium neurotoxicity: a report of five cases and a hypothesis about risk for neurotoxicity. *Am J Psychiatry* 1979; 136:963–966
21. Cutler NR, Post RM, Rey AC, et al: Depression-dependent dyskinesias in two cases of manic depressive illness. *N Engl J Med* 1981; 304:1088–1089
22. Petersdorf RG, Root RK: Alterations in body temperature, in *Harrison's Principles of Internal Medicine*, 11th ed. Edited by Braunwald E, Isselbacher KS, Petersdorf RG, et al. New York, McGraw-Hill, 1987
23. Weiner N: Atropine, scopolamine and related antimuscarinic drugs, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 7th ed. Edited by Gilman AG, Goodman LS, Rall TW, et al. New York, MacMillan, 1985
24. Schou M: Long-lasting neurological sequelae after lithium intoxication. *Acta Psychiatr Scand* 1984; 70:594–602

25. Sansone ME, Ziegler DK: Lithium toxicity: a review of neurologic complications. *Clin Neuropharmacol* 1985; 8:242-248
26. Addonizio G: Rapid induction of extra-pyramidal side effects with combined use of lithium and neuroleptics. *J Clin Psychopharmacol* 1985; 5:296-298
27. Sachdev PS: Lithium potentiation of neuroleptic-related extrapyramidal side effects (letter). *Am J Psychiatry* 1986; 143:942
28. Shopsin B, Gershon S: Cogwheel rigidity related to lithium maintenance. *Am J Psychiatry* 1975; 132:536-538
29. Kane J, Rifkin A, Quitkin F, et al: Extrapyramidal side effects with lithium treatment. *Am J Psychiatry* 1978; 135:851-853
30. Branchey MH, Charles J, Simpson GM: Extrapyramidal side effects in lithium maintenance therapy. *Am J Psychiatry* 1976; 133:444-445
31. Friedman E, Gershon S: Effect of lithium on brain dopamine. *Nature* 1973; 243:520-521
32. Kelwala S, Pomara N, Stanley M, et al: Lithium-induced accentuation of extra-pyramidal symptoms in individuals with Alzheimer's disease. *J Clin Psychiatry* 1984; 45:342-344
33. Price WA, Zimmer B: Lithium-induced akathisia. *J Clin Psychiatry* 1987; 48:48-81
34. Unger J, Decaux G, L'Hermite M: Rhabdomyolysis, acute renal failure, endocrine alterations and neurological sequelae in a case of lithium self-poisoning. *Acta Clin Belg* 1982; 37:216-223
35. Von Hartitzsch B, Hoenich NA, Leigh RJ, et al: Permanent neurological sequelae despite haemodialysis for lithium intoxication. *Br Med J* 1972; 4:757-759
36. Donaldson IM, Cunningham J: Persisting neurologic sequelae of lithium carbonate therapy. *Arch Neurol* 1983; 40:747-751
37. Nagaraja D, Taly AB, Sahu RN, et al: Permanent neurological sequelae due to lithium toxicity. *Clin Neurol Neurosurg* 1987; 89:31-34
38. Van der Velde CD: Toxicity of lithium carbonate in elderly patients. *Am J Psychiatry* 1971; 127:1075-1077
39. Lavender S, Brown JN, Berrill WT: Acute renal failure and lithium intoxication. *Postgrad Med J* 1973; 49:277-279
40. Speirs J, Hirsch SR: Severe lithium toxicity with normal serum concentrations. *Br Med J* 1978; 2:815-816
41. Hansen HE, Amdisen A: Lithium intoxication. *Q J Med* 1978; 47:123-144
42. Cohen WJ, Cohen NH: Lithium carbonate, haloperidol and irreversible brain damage. *JAMA* 1974; 230:1283-1287
43. Fricchione GL: Neuroleptic catatonia and its relationship to psychogenic catatonia. *Biol Psychiatry* 1985; 20:304-313
44. Derby IM: Manic-depressive "exhaustive" deaths. *Psychiatr Q* 1933; 7:436-449
45. Kraines SH: Bell's mania (acute delirium). *Am J Psychiatry* 1934; 91:29-40
46. Larson CP: Fatal cases of acute manic-depressive psychosis. *Am J Psychiatry* 1939; 95:971-982
47. Billig O, Freeman WT: Fatal catatonia. *Am J Psychiatry* 1944; 100:633-638
48. Shulack NR: Exhaustion syndrome in excited psychotic patients. *Am J Psychiatry* 1946; 102:466-475
49. Mann SC, Caroff SN, Bleier HR, et al: Lethal catatonia. *Am J Psychiatry* 1986; 143:1374-1381
50. Abrams R, Taylor MA: Catatonia: a prospective clinical study. *Arch Gen Psychiatry* 1976; 33:579-581
51. Caroff SN, Rosenberg H, Fletcher J, et al: Malignant hyperthermia susceptibility in neuroleptic malignant syndrome. *Anaesthesiology* 1987; 67:20-25
52. Coons DJ, Hillman FJ, Marshall RW: Treatment of neuroleptic malignant syndrome with dantrolene sodium: a case report. *Am J Psychiatry* 1982; 139:944-945
53. Granato JE, Stern BJ, Ringel A, et al: Neuroleptic malignant syndrome: successful treatment with dantrolene and bromocriptine. *Ann Neurol* 1983; 14:89-90
54. Goulon M, de Rohen-Chabot P, Elkharrat D, et al: Beneficial effects of dantrolene in the treatment of neuroleptic malignant syndrome: a report of two cases. *Neurology* 1983; 33:516-518
55. Bismuth C, de Rohen-Chabot P, Goulon M, et al: Dantrolene—a new therapeutic approach to the neuroleptic malignant syndrome. *Acta Neurol Scand (Suppl)* 1984; 100:193-198
56. Khan A, Jaffe JH, Nelson WH, et al: Resolution of neuroleptic malignant syndrome with dantrolene sodium: a case report. *J Clin Psychiatry* 1985; 46:244-246
57. Britt BA, Kalow W: Malignant hyperthermia: a statistical review. *Can Anaesth Soc J* 1970; 17:293-315
58. Britt BA: Etiology and pathophysiology of malignant hyperthermia. *Fed Proc* 1979; 38:44-48
59. Addonizio G, Susman VL: ECT as a treatment alternative for patients with symptoms of neuroleptic malignant syndrome. *J Clin Psychiatry* 1987; 48:102-105
60. Costini AM, Pitt HA, Gustafson AB, et al: Cardiovascular and metabolic manifestations of heat stroke and severe heat exhaustion. *Am J Med* 1979; 66:296-302
61. Sprung CH, Portocarrero CJ, Fernaine AU, et al: The metabolic and respiratory alteration of heat stroke. *Arch Intern Med* 1980; 140:665-669
62. Shalev A, Hermesh H, Munitz H: The role of external heat load in triggering the neuroleptic malignant syndrome. *Am J Psychiatry* 1988; 145:110-111
63. Klasing KC: Effect of inflammatory agents and interleukin I on iron and zinc metabolism. *Am J Physiol* 1984; 247:901-904
64. Taylor C, Rogers G, Goodman C, et al: Hematologic, iron-related and acute-phase protein responses to sustained strenuous exercise. *J Appl Physiol* 1987; 62:464-469
65. Syrkis I, Machtey I: Hypoferremia in acute myocardial infarction. *J Am Geriatr Soc* 1973; 20:28-30
66. Barash I, Djaldetti M: Ferrokinetic studies in acute myocardial infarction. *Am Heart J* 1975; 90:159-164
67. Fitzsimmons EJ, Kaplan K: Rapid drop in serum iron concentration in myocardial infarction. *Am J Clin Pathol* 1980; 73:552-555
68. Griffiths JD, Campbell LJ, Woodruff IW, et al: Acute changes in iron metabolism following myocardial infarction. *Am J Clin Pathol* 1985; 84:649-654
69. Youdim MB, Green AR, Bloomfield MR, et al: The effects of iron deficiency on brain biogenic monoamine biochemistry and function in rats. *Neuropharmacology* 1980; 19:259-267
70. Ashkenazi R, Ben-Shachar D, Youdim MB: Nutritional iron and dopamine binding sites in the rat brain. *Pharmacol Biochem Behav* 1982; 17(Suppl 1):43-47
71. Ben-Schachar D, Finberg JP, Youdim MB: Effect of iron chelators on dopamine D2 receptors. *J Neurochem* 1985; 45:999-1005
72. Rutledge JN, Hilal SK, Silver AJ, et al: Study of movement disorders and brain iron by MR. *AJR* 1987; 149:365-379
73. Knochel JP: Serum calcium derangements in rhabdomyolysis. *N Engl J Med* 1981; 305:161-162
74. Potts JT: Diseases of the parathyroid gland and other hypocalcemic disorders, in Harrison's Principles of Internal Medicine, 11th ed. Edited by Braunwald E, Isselbacher KS, Petersdorf RG, et al. New York, McGraw-Hill, 1987
75. Wintrobe MM, Lee RG, Boggs DR, et al: Clinical Hematology. Philadelphia, Lea & Febiger, 1981
76. Fricchione GL, Cassem NH, Hoobuman D, et al: Intravenous lorazepam in neuroleptic induced catatonia. *J Clin Psychopharmacol* 1983; 3:338-342

Changing Patterns of Neuroleptic Dosage Over a Decade

Gerard T. Reardon, Ph.D., Arthur Rifkin, M.D., Arthur Schwartz, M.D.,
Arthur Myerson, M.D., and Samuel G. Siris, M.D.

A study of patterns of neuroleptic dosage for 206 schizophrenic inpatients showed significant differences over time and among three centers—a general hospital psychiatric unit, a community mental health center, and a state hospital. In 1982 patients' mean dose at discharge was higher than the peak mean daily dose in 1973, and high-potency neuroleptics were being used almost exclusively. The mean length of stay decreased from 49 days in 1973 to 34 days in 1982. The possible relationship, if any, between increasing dosage, decreased length of stay, and the switch from low-potency to high-potency neuroleptics remains undetermined.

(Am J Psychiatry 1989; 146:726–729)

Numerous double-blind, controlled studies have documented the efficacy and safety of neuroleptic medications and set overall guidelines for their use (1–5). Within these guidelines, the effective range of doses for the treatment of acute psychosis has been found to be 400–1200 mg/day of chlorpromazine or the equivalent (4–7). Although it has been argued that rapid-loading doses of neuroleptics are useful in acute psychosis (8), this aspect of treatment is controversial, inasmuch as a number of controlled studies have not produced convincing evidence for the greater efficacy of this strategy (5), and no conclusive evidence has emerged that increasing neuroleptic dosage over the longer course of acute treatment benefits psychotic patients (9, 10). Nevertheless, it was our clinical impression that in the general prescribing practice of inpatient psychiatry, a gradual escalation of neuroleptic dosage had taken place over recent years. We therefore

undertook an investigation to document whether an increase in psychopharmacology had occurred and, if so, to what extent.

METHOD

To test the hypothesis that dosage has been increasing over time, the practices of three inpatient units—a voluntary nonprofit general hospital with an inpatient psychiatric service, a community mental health center (CMHC), and a state hospital—were chosen for review. All three facilities were affiliated with medical schools. We reviewed the cases of a preselected number (25 per year per center) of consecutively discharged inpatients in each center for the years 1973, 1977, and 1982, beginning in January of each year. A total of 532 charts were selected for possible review on the basis of computer-generated lists of discharge diagnoses that used the *DSM-II* criteria for the diagnoses of schizophrenia for the 1973 and 1977 samples and the *DSM-III* criteria for the 1982 sample. Charts were included if the patient had been diagnosed as having schizophrenia, was between the ages of 17.5 and 65 years, and had stayed in the hospital for at least 14 but not more than 120 days. For the state hospital sample, in addition, exclusion criteria were 1) patients could not have been transferred from other state hospitals and 2) they could not have had an extended pass to leave the inpatient unit (for 3 days or more). Patients from all three centers were included if they had received antiparkinsonian agents or benzodiazepines but were excluded if they had received antidepressants, lithium, or ECT.

For each patient the following data were collected by reviewing the chart record: age, sex, diagnosis, length of stay, and specific type and daily dose of antipsychotic for each day of hospitalization. Because of the number of different types of neuroleptics used, daily doses were converted for statistical analyses into chlorpromazine equivalents (11). Additionally, for patients who had received fluphenazine decanoate, before determining the chlorpromazine equivalents, we used the following method to convert to units of oral fluphenazine: 1 cc every 3 weeks of fluphenazine decanoate was equal to 25 mg/day of fluphenazine hydrochloride (12). Daily doses of antipsychotics were converted into weekly mean doses and an overall mean

Received July 19, 1985; revisions received Aug. 1 and Dec. 1, 1988; accepted Dec. 8, 1988. From the Departments of Psychiatry at Mount Sinai School of Medicine; at Queens Hospital Center, Jamaica, N.Y.; at University of Medicine and Dentistry, Robert Wood Johnson Medical School, Piscataway, N.J.; at Hahnemann Medical School, Philadelphia, Pa.; and at Hillside Division, Long Island Jewish-Hillside Medical Center, Glen Oaks, N.Y. Address reprint requests to Dr. Reardon, Department of Psychiatry, Mount Sinai School of Medicine, Box 1252, 5 East 98th St., New York, NY 10029.

Supported in part by NIMH grant MH-34309.

The authors thank the following persons for their contributions to data collection and analysis: Neil Birnbaum, Mark Hausdorf, Elaine Casey, Kathy Ridjowski, Lee Calamuci, and Richard Fagerstrom.

Copyright © 1989 American Psychiatric Association.

TABLE 1. Neuroleptic Doses and Length of Stay of 206 Schizophrenic Patients at Three Centers in 3 Different Years

								Patients Taking Low- Potency Neuro- leptics		Patients Taking High- Potency Neuro- leptics					
Dose (chlorpromazine equivalents)												Patients' Age (years)		Length of Stay (days)	
		Daily		Peak		At Discharge									
Year and Center	N	Mean	SD	Mean	SD	Mean	SD	N	%	N	%	Mean	SD	Mean	SD
1973															
General hospital	25	897	455	1392	825	942	484	24	96	18	82	28	9	53	21
CMHC	16	546	524	827	658	523	423	14	88	14	88	23	6	60	37
State hospital	15	1027	661	1752	1316	1155	1356	12	80	12	80	31	12	30	16
Overall	56	832	559	1327	990	880	832	50	89	44	79	28	9	49	29
1977															
General hospital	25	1107	814	1789	1384	1303	1269	18	72	15	60	29	11	36	19
CMHC	25	1288	815	2157	1281	1360	882	7	28	21	84	29	9	37	16
State hospital	25	1831	1244	2694	1834	1699	1471	18	25	18	72	33	10	35	16
Overall	75	1408	1014	2213	1544	1454	1228	43	57	54	72	30	10	37	15
1982															
General hospital	25	1849	1455	3000	2228	2000	1947	6	24	22	88	30	9	30	15
CMHC	25	1064	788	1813	1629	1369	1282	10	40	22	88	27	6	35	16
State hospital	25	2159	2479	3147	3331	2286	3054	12	48	22	88	34	9	36	20
Overall	75	1691	1760	2653	2536	1885	2222	28	37	66	88	30	9	34	17

dose for the entire length of stay. The peak daily dose and the dose of neuroleptic the patient was receiving at the time of discharge were also recorded.

RESULTS

The cases of 206 patients (113 male and 93 female) were selected for the study sample. Chi-square analysis demonstrated no significant differences by sex among patients at the three centers ($\chi^2=0.45$, $df=2$, $p=0.80$). There were differences among the centers in the reason why patients were excluded from the data analysis. The CMHC was more likely to have treated patients with either antidepressants or lithium. The general hospital psychiatric unit was more likely to have treated patients with ECT. Leave without a physician's consent and extended passes occurred only at the state psychiatric center.

Other cases were ruled out because of medical record coding errors (e.g., a patient did not have a diagnosis of schizophrenia, or after reviewing the chart, we decided that the diagnosis of schizophrenia was clearly out of the question, for example, a case of steroid-induced psychosis which remitted 2 days after the steroids were discontinued). Although some of the cases, especially in the 1972 sample, would now be considered affective disorders, we included them in the sample because in the opinion of the physicians at the time, the patients had schizophrenia. Because the CMHC and the state hospital opened in 1972, the number of eligible cases was 16 and 15, respectively, for the 1973 index year.

As shown in table 1, the overall mean dose doubled at each center between 1973 and 1982. Because of the variability in dosage within the sample, the chlorpromazine-equivalent doses were converted into loga-

rithm values for statistical analyses. Two-way analysis of variance (ANOVA) was used to determine the main effects for center and year and the interaction between center and year. There were statistically significant differences among the centers ($F=9.36$, $df=2$, 197 , $p<0.0001$) and across years ($F=11.37$, $df=2$, 197 , $p<0.0001$). There was a trend for significant interaction between year and center ($F=2.14$, $df=4$, 197 , $p<0.08$). Two-way ANOVAs revealed the same pattern of significant increases for peak dose ($F=5.46$, $df=8$, 197 , $p<0.0001$) and discharge dose ($F=3.46$, $df=8$, 197 , $p<0.0009$). Generally, the CMHC gave the lowest doses, while the state hospital gave the highest.

Some readers may question whether the inclusion of patients who had received fluphenazine decanoate led to higher mean doses in 1982 because of the conversion formula we used to determine chlorpromazine equivalents and because more patients received this drug in 1982. We reanalyzed the data excluding the patients who received decanoate ($N=27$) and found essentially the same results. Overall, the two-way ANOVA demonstrated that there was still a significant increase in daily mean dose ($F=5.46$, $df=8$, 170 , $p<0.0001$). In addition, there was a significant main effect for center ($F=6.51$, $df=2$, 170 , $p<0.002$) and for year ($F=9.88$, $df=2$, 170 , $p<0.0001$) and an interaction between year and center ($F=3.36$, $df=4$, 170 , $p<0.01$). There was a dramatic increase in mean dose between 1973 and 1977 at the state hospital and at the CMHC. In contrast, in the general hospital most of the increase occurred between 1977 and 1982. In terms of peak dose, the overall two-way ANOVA was significant ($F=5.51$, $df=2$, 170 , $p<0.0001$), with no difference among the centers but significantly higher doses between 1973 and 1982. The highest peak doses for the general hospital and the state hospital occurred in

1982, while the highest peak dose for the CMHC was in 1977.

An additional indication of the strength of the findings is seen in the change over time in the mean daily discharge dose. For example, in the general hospital psychiatric unit, the mean \pm SD discharge dose in 1982 was 2000.0 ± 1947.2 mg/day. This was substantially above the peak mean dose in 1973 at the same facility (1391.6 ± 824.8 mg/day). This trend was also true of the other two facilities.

There were other significant differences over time and between centers. Post hoc differences in length of stay within each center were tested by using Tukey's Studentized range test, with significance set at 0.05. The mean \pm SD length of stay for the hospital psychiatric unit had decreased significantly between 1973 and 1982 from 52.6 ± 21.3 days to 29.7 ± 15.3 days; for the CMHC it had decreased from 60.1 ± 37.2 days to 34.7 ± 15.9 days. In contrast, the mean length of stay at the state hospital had increased from 29.7 ± 16.0 days to 36.5 ± 20.4 days; however, this increase was not statistically significant.

A two-way ANOVA indicated a statistically significant difference in patients' ages across the three centers ($F=6.96$, $df=2$, 197 , $p<0.001$) and a trend for significant change in ages over years ($F=2.53$, $df=2$, 197 , $p<0.08$) but no interaction between center and year ($F=0.59$, $df=4$, 97 , $p<0.67$).

There were a number of other changes in the pattern of prescribing neuroleptics. For example, the practice of prescribing two different neuroleptics concomitantly, a frequent occurrence in 1973, had all but disappeared by 1982. Another interesting trend was the shift from low-potency drugs. It is difficult to obtain an accurate picture of this phenomenon, since physicians frequently prescribed two neuroleptics (one high-potency and one low-potency) at the same time or two neuroleptics in a "serial" fashion (e.g., chlorpromazine for the first 2 weeks of hospitalization and fluphenazine during the third week of hospitalization). Nonetheless, it is clear from table 1 that there was a dramatic decrease in the percentage of patients who received low-potency neuroleptics from 1973 to 1982.

The tendency to prescribe both high- and low-potency neuroleptics during the index hospitalization made it difficult to test whether the increase in neuroleptic dosage was due to a shift from low-potency to high-potency drugs. However, we did compare the data on the patients treated only with low-potency neuroleptics (chlorpromazine or thioridazine) and the data on the patients who received only high-potency neuroleptics. The overall mean \pm SD dose for patients treated with low-potency neuroleptics in 1973 ($N=8$) was 926.4 ± 657.4 mg/day; in 1977 it was 920.3 ± 575.3 mg/day ($N=17$); and in 1982 it was 741.6 ± 376.4 mg/day ($N=8$). In contrast, only one patient in 1973 received a high-potency neuroleptic only, and the overall mean dose was 554.0 mg/day. In 1977 the overall mean dose for those who received high-potency neuroleptics only ($N=9$) was 1149.2 ± 865.0 mg/day;

in 1982 the mean dose of high-potency neuroleptics was 1785.6 ± 1247.9 mg/day ($N=22$). None of the means were significantly different from one another. One should be cautious in interpreting these results, however, because of the small sample size and the variability in dosage within these subgroups.

DISCUSSION

Our findings confirm the existence of a significant increase in the dosage patterns of neuroleptic medication over the decade from the 1970s to the 1980s: higher equivalent doses of antipsychotic drugs were being given in 1982 than were given before. We do not know for sure what accounted for this phenomenon. Since we relied on chart diagnoses made by many different clinicians who used varying criteria for schizophrenia, some of the subjects may not have met the *DSM-III* criteria. However, since this investigation concerned the prescribing practices of these clinicians, the working clinical diagnoses at the time are relevant, not the diagnoses that might have been given by other clinicians using different criteria.

The validity of the criteria for converting doses of several neuroleptics to chlorpromazine-equivalent units is not firmly established, and this may have decreased the accuracy of our findings. Davis (13) has shown, however, that the criteria used here for chlorpromazine equivalents approximate closely the doses prescribed blindly by investigators in many clinical trials. Although the conversions may not be numerically precise, the magnitude of the increase in dosage (i.e., a doubling) that we have demonstrated supports the hypothesis that many clinicians have been treating schizophrenia with much higher doses of antipsychotics than in previous years. Baldessarini et al. (14), in a study examining dosing practices, found that mean chlorpromazine-equivalent doses of haloperidol (the most commonly prescribed neuroleptic in our 1982 sample) were almost three times as high as doses of chlorpromazine. Other recent reports (15, 16) have also emphasized that most schizophrenic patients do well on moderate doses of neuroleptics, and there is some preliminary evidence that higher doses of low-potency neuroleptics may lead to less positive clinical response and more side effects.

The phenomenon of increasing dosage and decreasing length of stay at two of the facilities suggests that there may be a relationship between dosage and length of stay. Physicians feeling pressure to discharge patients may believe that increasing the dose of antipsychotic will lead to a more rapid remission. The literature on the efficacy of rapid neuroleptization and acute high-dose neuroleptic treatment is controversial (17), but the beneficial effects of unusually high doses of neuroleptics have not been confirmed, so it is unlikely that the shorter stays we observed in the later years were a result of the higher drug doses the patients had received.

The clinical staffs of the general hospital and the CMHC had the impression that the patients being treated in these facilities in 1982 were "more chronically ill" than those seen 10 years earlier. This observation is consistent with reports in the literature (18–20) that the locus of care for the chronically mentally ill has shifted from state hospitals to acute care facilities. What has not been documented, however, is whether patients need or benefit from such high doses of neuroleptics. When the charts of the patients in the 1982 sample who received the five highest doses at the general hospital were examined by one of us (G.T.R.), it was found that three of these patients had repeatedly made threats to physically harm the staff (although no one had actually struck a staff member or other patient). In addition, the chart notes demonstrated that the staff had been frustrated by their lack of a more robust response to medication. In contrast, the patients who received the lowest doses were seen as having made marked improvement and often were described as "friendly," "cooperative," or "appreciative of staff efforts."

Another possible explanation for our findings may lie in the shift from low-potency to high-potency antipsychotics. The conversions we used refer to antipsychotic potency, not sedative potency, yet sedation may be of value in controlling agitated and overly aggressive behavior, even if it is ineffective in ameliorating psychotic symptoms. With the change to high-potency antipsychotics, higher doses may have to be given in order to obtain a level of sedation previously achieved by lower doses of the low-potency neuroleptics. Alternatively, side effects of the lower-potency neuroleptics (not just sedation but also orthostatic hypotension, constipation, dry mouth, and blurry vision) may have limited dosing in the earlier years.

This study confirms the impression of many clinicians and investigators that higher doses of antipsychotics are being routinely used. It is unclear whether more is better. To address this issue, we recommend research such as comparing several doses of neuroleptics or investigating concomitant use of sedatives. It is clear that the marked increase in dosage that we found in these three hospitals, which presumably is representative of practice in similar institutions, was not the result of a change in clinical practice based on new research data. Such an important change in routine

clinical practice should be validated. Higher doses of neuroleptics should not be used unless there is a definite indication.

REFERENCES

1. Cole JO, Davis JM: Organic therapies, in *Comprehensive Textbook of Psychiatry*, 2nd ed, vol 2. Edited by Freedman AM, Kaplan HI, Sadock BJ. Baltimore, Williams & Wilkins, 1975
2. Hogarty GE, Goldberg SC, Schooler NR: Drug and psychotherapy in the aftercare of schizophrenic patients, III: adjustment of nonrelapsed patients. *Arch Gen Psychiatry* 1974; 31:609–618
3. Klein DF, Gittelman R, Quitkin F, et al: *Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children*, 2nd ed. Baltimore, Williams & Wilkins, 1980
4. Kessler KA, Waletzky JP: Clinical use of the antipsychotics. *Am J Psychiatry* 1981; 138:202–209
5. Siris SG, Rifkin A: Drug treatment of acute schizophrenia, in *Schizophrenia and Affective Disorders: Biology and Drug Treatment*. Edited by Rifkin A. Boston, John Wright-PSG, 1983
6. Davis JM: Overview: maintenance therapy in psychiatry, I: schizophrenia. *Am J Psychiatry* 1975; 132:1237–1245
7. Klerman GL: Drug therapy of schizophrenia, I: nature of the disorder and the drugs used in the treatment. *Drug Therapy* 1973; 3:94–106
8. Donlon PT, Hopkin J, Tupin JP: Overview: efficacy and safety of the rapid neuroleptization method with injectable haloperidol. *Am J Psychiatry* 1979; 136:273–278
9. Cole J: Psychopharmacology update, antipsychotic drugs: is more better? *McLean Hospital J* 1982; 7:61–87
10. Linden R, Davis JM, Rubinstein J: High vs low dose treatment with antipsychotic agents. *Psychiatr Annals* 1982; 12:769–781
11. Schooler NR, Levine J, Severe JB, et al: Prevention of relapse in schizophrenia: an evaluation of fluphenazine decanoate. *Arch Gen Psychiatry* 1980; 37:16–24
12. *AMA Drug Evaluations*, 5th ed. New York, American Medical Association, 1980
13. Davis JM: Comparative doses and costs of antipsychotic medication. *Arch Gen Psychiatry* 1976; 33:858–861
14. Baldessarini RJ, Katz B, Cotton P: Dissimilar dosing with high-potency and low-potency neuroleptics. *Am J Psychiatry* 1984; 141:748–752
15. Baldessarini RJ, Cohen BM, Teicher MH: Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Arch Gen Psychiatry* 1988; 46:79–91
16. Hayes G, Sramek J: Dosing practices for high- and low-potency neuroleptics (letter). *Am J Psychiatry* 1988; 145:769
17. Aubree JC, Leder MH: High and very high dosage antipsychotics: a critical review. *J Clin Psychiatry* 1980; 41:341–350
18. Greenhill MH: Psychiatric units in general hospitals: 1979. *Hosp Community Psychiatry* 1979; 30:169–182
19. Bachrach LL: General hospital psychiatry: overview from a sociological perspective. *Am J Psychiatry* 1981; 138:879–887
20. Greenblatt M, Glazier E: The phasing out of mental hospitals in the United States. *Am J Psychiatry* 1975; 132:1135–1140

Serotonergic Measures in the Brains of Suicide Victims: 5-HT₂ Binding Sites in the Frontal Cortex of Suicide Victims and Control Subjects

Ramesh C. Arora, Ph.D., and Herbert Y. Meltzer, M.D.

The authors determined serotonin₂ (5-HT₂) binding in the frontal cortex of 32 suicide victims and 37 subjects who died from nonpsychiatric causes. The maximum number of binding sites (B_{max}) and the affinity (K_d) were significantly higher in subjects who had committed suicide than in control subjects. However, there was no difference in K_d between these two groups after the influence of age, race, sex, and postmortem delay was covaried. The B_{max} of subjects who had committed violent suicide was significantly greater than that of control subjects.

(Am J Psychiatry 1989; 146:730-736)

There is extensive evidence suggesting that among the biological factors predisposing to suicide, serotonin (5-HT) may be of special importance. The major evidence for this is the lower concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT in CSF, in suicide victims, particularly those who committed suicide using violent methods (1, 2). This has been reported in at least seven studies (3-10), but one study (11) did not find lower 5-HIAA levels in suicide victims. Lower concentrations of CSF 5-HIAA are also present in some suicidal patients with histories of aggression (4), arsonists (12), and suicidal patients with schizophrenia (7, 8).

Four types of studies have examined serotonergic measures in the brains of suicide victims. Lower levels of 5-HT (13-15) and 5-HIAA (16) have been reported in the midbrain raphe region of suicide victims than in those of control subjects, but no consistent changes

have been observed in many forebrain areas and nuclei (15, 17, 18). Studies by Owen et al. (19), Stanley et al. (20), Crow et al. (21), and Arato et al. (22) also did not observe any significant difference in 5-HT or 5-HIAA levels in the frontal cortex of suicide victims compared with age-matched control subjects. Korpi et al. (23) observed lower 5-HT levels in the hypothalamus and higher 5-HT levels in the globus pallidus and putamen of suicide victims. The number of subjects in their study was small, however, and there was no correction for the large number of statistical tests carried out. We recently found no difference in the levels of 5-HIAA in the frontal cortex of 28 suicide victims compared with those of 73 control subjects (unpublished paper of Ohmori and Meltzer).

[³H]Imipramine binding sites may be allosteric regulators of the 5-HT uptake sites and may provide a measure of the density of presynaptic serotonergic neurons (24, 25). Their number has been reported to be lower (26, 27), not significantly different (21, 28; our unpublished observations), or higher (29) in postmortem brain specimens from suicide victims. Arato et al. (22) studied [³H]imipramine binding in the right and left sides of the frontal cortex in suicide victims and normal control subjects. They found a significantly higher maximum number of binding sites (B_{max}) in the left hemisphere of suicide victims than in the right but higher B_{max} in the right hemisphere than in the left in normal control subjects. The right-left B_{max} ratio was significantly lower in suicide victims than in control subjects.

Two groups (19, 21, 28, 30) have found no difference in [³H]5-HT binding (5-HT₁ receptors) between suicide victims and normal control subjects. Matsubara and Meltzer (unpublished paper) have found that the B_{max} of 5-HT_{1A} sites of victims of suicide by non-violent means was significantly greater than that of normal control subjects but not significantly different from that of victims of suicide by violent means. Stanley and Mann (31) reported a significantly higher (44%) B_{max} of 5-HT₂ sites in the frontal cortex of 11 suicide victims than in the frontal cortex of 11 age- and sex-matched control subjects who had died of cardiovascular disease or in motor accidents. Mann et al. (30) subsequently reported similar results (a 28%

Received April 4, 1988; revision received Oct. 25, 1988; accepted Dec. 1, 1988. From the Laboratory of Biological Psychiatry, Department of Psychiatry, Case Western Reserve University School of Medicine. Address reprint requests to Dr. Arora, Laboratory of Biological Psychiatry, Case Western Reserve University, 2040 Abington Rd., Cleveland, OH 44106.

Supported, in part, by NIMH grant MH-41594, NIMH Research Scientist Award MH-47808 to Dr. Meltzer, the Cleveland Foundation, and the Sawyer Foundation.

The authors thank the staff of the Cuyahoga County Coroner's Office, Cleveland, for providing postmortem brain samples, Ms. Lisa Kregel for technical help, and Mrs. Jar Chi Lee for data analysis.

Copyright © 1989 American Psychiatric Association.

higher B_{max}) in 13 subjects who committed suicide by violent means. They did not find any difference in the affinity (K_d) for 5-HT between the two groups. Contrary to this, Owen et al. (19, 28) and Crow et al. (21) did not find any difference in 5-HT₂ binding between suicide victims and age-matched control subjects. McKeith et al. (32) recently reported nonsignificantly higher 5-HT₁ and 5-HT₂ binding in the frontal cortex of patients with major affective disorders than in normal control subjects.

In the present study, we determined 5-HT₂ binding in the frontal cortex of subjects who committed violent or nonviolent suicide compared with age- and sex-matched control subjects who died of medical diseases or by accidental means.

METHOD

Samples of frontal cortex (Brodman's areas 8 and 9) from 37 nonpsychiatric control subjects (25 men and 12 women) and 32 suicide victims (22 men and 10 women) were obtained at autopsy from the Cuyahoga County Coroner's Office, Cleveland. The medical examiner determined the cause of death. Sixteen of the nonpsychiatric control subjects died of myocardial infarctions, two of other heart diseases, seven of pulmonary emboli or other pulmonary diseases, four of accidental carbon monoxide poisoning, two of renal failure, four in motor vehicle or other accidents, one of asthma, and one of asphyxia. Suicide victims were divided into two subcategories: 21 who had committed violent suicide and 11 who had committed nonviolent suicide. The violent suicide group included 12 subjects who committed suicide by hanging, seven by shooting, one by stabbing, and one by jumping from a great height. The nonviolent suicide group included six who committed suicide by carbon monoxide intoxication and five from drug overdose. Insufficient data were available from police and the coroner's office to assign psychiatric diagnoses to the suicide victims. There were no significant differences (Student's *t* test) between the suicide victims and the control subjects with respect to age or the time elapsed between death and autopsy (postmortem delay). The mean \pm SD age of the suicide victims was 48.1 ± 20.5 years (range=20–87); for the control subjects it was 45.3 ± 16.9 (range=21–83). The mean postmortem delay for the suicide victims was 15.3 ± 7.5 hours (range=2.0–26.5); for the control subjects it was 13.8 ± 7.4 (range=3.0–32.0).

Specimens from suicide victims and control subjects were assayed on a blind basis in pairs matched for age and sex as closely as possible. (The sample included one unpaired control subject.) The mean age difference between the 16 pairs of suicide victims and the 18 pairs of control subjects was 7.12 ± 5.89 years.

The frontal cortex was homogenized by polytron (setting=7, 15 seconds) in 50 volumes (weight per volume, w/v) of 50 mM of tromethamine (tris) hydrochloride (pH=7.4 at 25 °C) containing 120 mM of sodium

chloride plus 5 mM of potassium chloride. The homogenate was centrifuged at 40,000 *g* for 10 minutes at 0–4 °C. The resulting pellet was resuspended in the same buffer and centrifuged twice. After the last centrifugation, the pellet was resuspended in the same buffer (40 ml w/v) for binding studies.

We measured 5-HT₂ binding using [³H]spiperone as a binding ligand following a modification of the method of Creese and Snyder (33). In brief, 0.2 ml of membrane preparation was incubated with [³H]spiperone (specific activity=16.4 Ci/nmol) at 37 °C for 20 minutes in 50 mM of tris hydrochloride (pH=7.4) containing 120 mM of sodium chloride, 5 mM of potassium chloride, and 0.1% of ascorbic acid, in the presence and absence of cinanserin (10 μ M) to define specific binding. After incubation, the reaction was terminated by the addition of cold tris hydrochloride plus sodium chloride plus potassium chloride buffer and filtered rapidly through glass fiber filters. The filters were washed with 3 \times 4 ml of the same buffer, and then the filters were transferred to counting vials containing 10 ml of a liquid scintillation cocktail (Budget-Solv, Research Products International, Chicago) and counted after overnight digestion. Binding was quantified per mg of protein of the membrane suspension as assayed by the method of Lowry et al. (34). The specific binding of [³H]spiperone was defined as the difference in binding in the presence and absence of cinanserin. The coefficient of variation for duplicate determinations of K_d and B_{max} was less than 10%, indicating that assay reliability was acceptable.

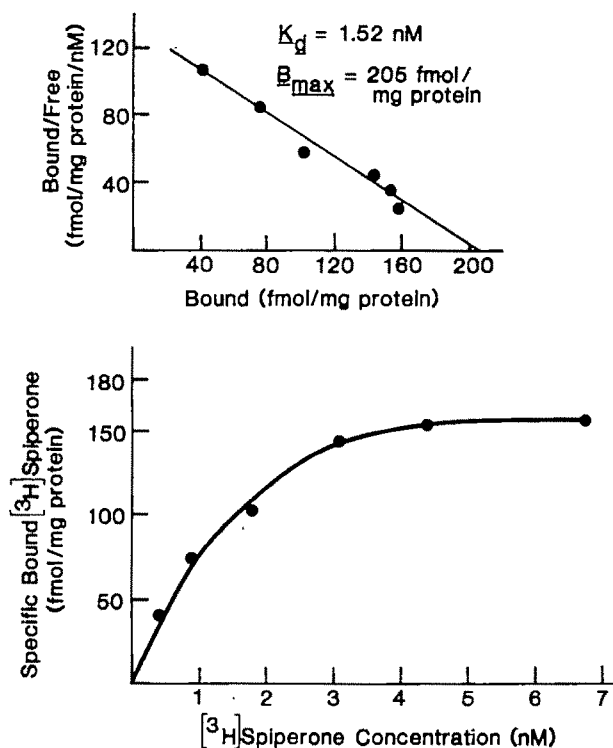
[³H]Spiperone was purchased from New England Nuclear, Boston. Cinanserin was a gift from E.R. Squibb and Sons, Inc. Other chemicals used were of analytical-grade quality. All results are given in mean \pm SD.

RESULTS

The specific binding of [³H]spiperone to human frontal cortex was saturable. A Scatchard plot of the saturation data gave a straight line, indicating the presence of a single population of [³H]spiperone binding sites in human frontal cortex (figure 1). Specific binding averaged 35%–55% for the concentrations of [³H]spiperone used in this study. The mean B_{max} and K_d for the 37 control subjects and the 32 suicide victims are shown in table 1. The B_{max} and K_d were significantly correlated with each other in the normal control subjects ($\rho=0.46$, $N=37$, $p=0.0041$) and the suicide victims ($\rho=0.48$, $N=32$, $p=0.0049$).

The relationship between B_{max} and K_d of [³H]spiperone binding in the frontal cortex of suicide victims and control subjects without adjustment for age, sex, race, and postmortem delay was examined first. B_{max} and K_d were significantly higher in suicide victims than in control subjects ($t=3.11$, $df=67$, $p=0.0028$ and $t=2.26$, $df=67$, $p=0.027$, respectively). We next examined each of the four factors individually.

FIGURE 1. [³H]Spiperone Binding in the Frontal Cortex of One Normal Control Subject as a Function of Increasing Concentrations of [³H]Spiperone^a



^aThe top panel is a Scatchard plot of [³H]spiperone binding.

TABLE 1. [³H]Spiperone Binding in the Frontal Cortex of Normal Control Subjects and Suicide Victims

Group	B_{max} (fmol/mg protein)		K_d (nM)	
	Mean	SD	Mean	SD
Normal control subjects (N=37)	199.2	84.9	1.59	0.67
Suicide victims (N=32)	268.4	100.1	2.03	0.93
Violent suicide (N=21)	287.9	102.9	2.04	0.82
Nonviolent suicide (N=11)	231.1	86.8	2.01	1.14

There was a trend for the 47 men to have a higher B_{max} (243.7 ± 108.99 fmol/mg protein) than the 22 women (204.6 ± 17.9) (approximate $t=1.88$, approximate $df=64$, $p=0.06$). Although there was no difference in age between suicide victims and control subjects, the 47 men in the study (42.5 ± 17.9 years old) were significantly younger than the 22 women (55.3 ± 17.2 years old) ($t=2.79$, $df=67$, $p<0.007$). There was a significant relationship between age and sex ($\rho=0.33$, $N=69$, $p=0.006$). There was a trend toward a negative correlation between age and B_{max} in female control subjects ($\rho=-0.539$, $N=12$, $p=0.071$). There was no relationship between B_{max} or K_d and postmortem delay or race (data not presented).

Analysis of covariance (ANCOVA) with sex, group-by-sex interaction, age, race, and postmortem delay as covariates indicated significantly higher mean B_{max} in suicide victims than in control subjects (table 2 and figure 2). There was a significant sex effect but no interaction between group and sex (table 2). The least-square mean values of B_{max} adjusted for age, sex, race, and postmortem delay were 265.9 ± 21.3 fmol/mg protein for all suicide victims, 198.7 ± 16.3 for all control subjects, 264.6 ± 18.5 for all men, and 200.0 ± 20.7 for all women. Effects of race, age, and postmortem delay on B_{max} were not significant. ANCOVA with sex, group-by-sex interaction, race, age, and postmortem delay did not indicate any difference in K_d value between suicide victims and control subjects.

We next compared B_{max} and K_d in the 21 victims of violent suicide, the 11 victims of nonviolent suicide, and the 37 control subjects. B_{max} with sex, group-by-sex interaction, race, age, and postmortem delay as covariates was significantly higher in victims of violent suicide than in control subjects (table 2 and figure 3). No difference in B_{max} was noted between victims of violent and nonviolent suicide or between victims of nonviolent suicide and control subjects. There was a significant sex effect on B_{max} (table 2): it was significantly higher in men than women. ANCOVA with sex, group-by-sex interaction, race, age, and postmortem delay as covariates did not indicate any difference in K_d value between control subjects, victims of violent suicide, and victims of nonviolent suicide (table 2).

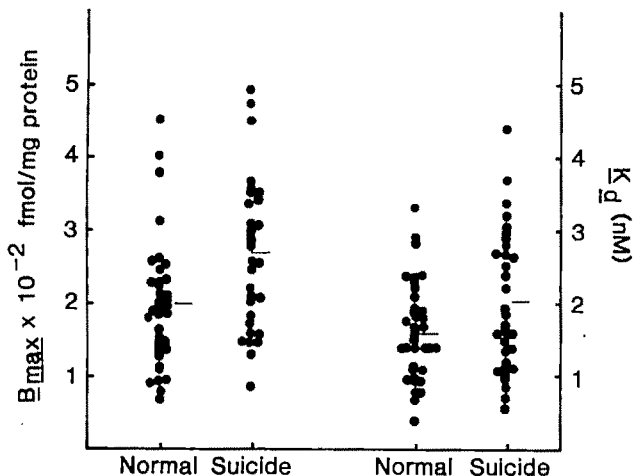
We also performed saturation studies using [³H]ketanserin, a selective ligand for 5-HT₂ receptors (35, 36), following the method of Stockmeier and Kellar (37). The B_{max} identified in four normal control subjects with [³H]ketanserin (224.9 ± 34.7 fmol/mg protein) and [³H]spiperone (213.2 ± 28.9 fmol/mg protein) as ligands were comparable. The same was true in four suicide victims (265.5 ± 56.9 and 272.9 ± 83.4 fmol/mg protein, respectively).

DISCUSSION

The results reported here suggest that the maximum number of [³H]spiperone binding sites in the frontal cortex of suicide victims is significantly greater than that of control subjects who died of medical causes such as myocardial infarction or in accidents. B_{max} in victims of violent suicide but not in victims of nonviolent suicide was significantly greater than that in normal control subjects. We found no significant difference between victims of violent and nonviolent suicide, suggesting that it is premature to conclude that greater 5-HT₂ binding in the frontal cortex is present only in victims of violent suicide. There was a significant sex effect on B_{max} : men had higher B_{max} than women. The K_d (an inverse measure of affinity for [³H]spiperone) was also higher in the frontal cortex of suicide victims than in that of control subjects. However, the differ-

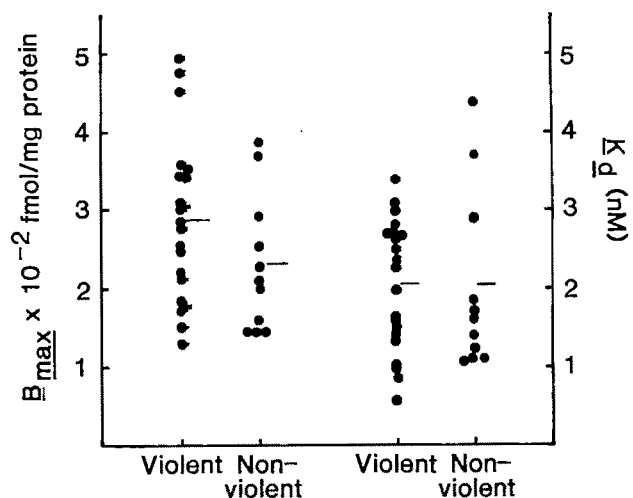
TABLE 2. Results of Analysis of Covariance of [³H]Spiperone Binding in the Frontal Cortex of Normal Control Subjects, Victims of Violent Suicide, and Victims of Nonviolent Suicide

Groups Compared and Variable	df	B_{max}		K_d	
		F	p	F	p
Control subjects (N=37) versus all suicide victims (N=32)					
Group	1, 62	6.89	<0.011	2.07	<0.155
Sex	1, 62	5.49	<0.022	0.08	<0.779
Group-by-sex interaction	1, 62	0.72	<0.400	0.46	<0.502
Race	1, 62	1.32	<0.254	0.36	<0.549
Age	1, 62	1.83	<0.181	0.53	<0.470
Postmortem delay	1, 62	0.58	<0.450	0.69	<0.408
Control subjects (N=37) versus victims of violent suicide (N=21) versus victims of nonviolent suicide (N=11)					
Group	2, 60	4.01	<0.023	1.03	<0.363
Sex	1, 60	4.50	<0.038	0.00	<0.997
Group-by-sex interaction	2, 60	0.29	<0.747	0.30	<0.739
Race	1, 60	0.94	<0.337	0.42	<0.520
Age	1, 60	1.26	<0.266	0.45	<0.507
Postmortem delay	1, 60	0.34	<0.563	0.72	<0.400

FIGURE 2. B_{max} and K_d of [³H]Spiperone Binding in the Frontal Cortex of 37 Normal Control Subjects and 32 Suicide Victims^a^aHorizontal lines represent mean values.

ence in K_d disappeared after we covaried the influence of age, race, sex, and postmortem delay.

Before discussing these findings further, it is important to consider the nature of [³H]spiperone binding in the frontal cortex and some aspects of the samples. At 37 °C, specific [³H]spiperone binding, determined as the difference between binding in the presence and absence of 10 μ M cinanserin, represented 35%–55% of total binding. Scatchard analysis revealed only a single site. Displacement studies with known 5-HT antagonists as well as other drugs (38) indicate that this site is a 5-HT₂ site, although [³H]spiperone will also bind to other neurotransmitter sites, such as dopamine₂ and α_1 -adrenergic receptor sites. There are no known or demonstrated dopamine-2 receptor sites in the human frontal cortex (39). The evidence from rat (40) and human (38) studies strongly suggests that [³H]spiperone labels 5-HT₂ receptor sites in the frontal cortex. Further, binding studies using ketanserin or

FIGURE 3. B_{max} and K_d of [³H]Spiperone Binding in the Frontal Cortex of 22 Victims of Violent Suicide and 11 Victims of Nonviolent Suicide^a^aHorizontal lines represent mean values.

spiperone ligands yielded similar values in normal subjects and suicide victims, also suggesting that [³H]spiperone labels 5-HT₂ receptor sites in the frontal cortex.

The B_{max} we observed in our control subjects was 100% greater than that reported by Mann et al. (30) (199.2 ± 84.9 fmol/mg protein versus 99.6 ± 11.1 fmol/mg protein, respectively). Both we and they used Brodmann's areas 8 and 9. Slight differences in dissection and assay method may have contributed to this difference. For example, they used 4 mM of calcium chloride and we used 5 mM of potassium chloride. Autoradiographic studies (41) indicate that there is a large variation in 5-HT₂ binding among different cortical layers. The finding is valid irrespective of the cortex area. Further, low values for binding will be found when white matter that is virtually devoid of 5-HT₂

binding is present in membrane preparation. The K_d of our normal control subjects was 1.59 nM, but that of the subjects of Mann et al. (30) was 0.9 nM. This may also be due to differences in assay method. The higher K_d value we observed was not due to administration of drugs that bind to or affect 5-HT₂ receptors before death: there was no evidence by history and toxicological studies that the control subjects were taking such drugs. Our values for K_d (1.59 nM) and B_{max} (199.2 fmol/mg protein) were similar to those reported by Marcusson et al. (42) (1.2 nM and 258 fmol/mg per protein, respectively).

The higher value for B_{max} in our suicide victims was due to higher levels of B_{max} in the suicide victims who used violent means, such as shooting or hanging, rather than nonviolent means, such as a drug overdose. Mann et al. (30) studied only individuals who had committed suicide by violent means. However, we noted no difference in B_{max} between our victims of violent and nonviolent suicide. The greater B_{max} was not associated with any change in K_d , so it is unlikely that this reflects greater 5-HT₂ binding.

Several possible factors could contribute to the difference between our results and those of Owen et al. (19, 28) and Crow et al. (21). First, these authors studied binding at a single concentration (subsaturating) of the ligand ketanserin. Second, different areas of the frontal cortex were used in these studies: Brodmann's area 10 was used by Crow et al. (21) and the frontal cortex was used by Owen et al. (28). Finally, there may have been too few subjects in our study to detect a difference in B_{max} between victims of violent and nonviolent suicide. For an alpha level of 0.05, our study had a power of 0.38 to detect a difference between victims of violent and nonviolent suicide. To achieve a power of 0.80, at an alpha level of 0.05, 44 subjects in each group would be needed. The mean size difference of 56.8 fmol/mg protein in B_{max} between the two groups was compared. However, 21 subjects would be needed to find a significant difference between control subjects, victims of violent suicide, and victims of nonviolent suicide. Further studies should include larger sample sizes to ensure sufficient statistical power. Furthermore, caution is needed in comparing data from this study with those from other studies because of possible differences in the binding assay.

Toxicological studies of the brains of our suicide victims did not indicate the presence of any antidepressant drugs except for one suicide victim who had taken amitriptyline and nortriptyline. Chronic administration of antidepressant to rats has been reported (43) to down-regulate the density of 5-HT₂ receptors. Therefore, the greater density of 5-HT₂ receptors observed in this study should not have been due to drug treatment. There was no correlation between postmortem delay (3–32 hours in this study) and K_d or B_{max} of 5-HT₂. Other investigators (28, 30–32) have also not found any correlations between postmortem delay and binding constants of [³H]spiperone in the frontal cortex.

Is the up-regulation of 5-HT₂ receptors that has been confirmed in this study related to violent suicide? Animal studies (37, 44, 45) have indicated that 12 days of reserpine administration or ECT raises 5-HT₂ binding in the rat frontal cortex. None of the suicide victims in the present study received reserpine or ECT in the period before death according to information available from the coroner. As we mentioned at the beginning of this paper, violent suicide has been related to lower serotonergic activity. The up-regulation of 5-HT₂ receptors due to reserpine could be due to decreased serotonergic activity. However, depletion of 5-HT by 5,7-dihydroxytryptamine-induced lesions of the midbrain raphe or by parachlorophenylalanine, an inhibitor of tryptophan hydroxylase, did not up-regulate 5-HT₂ receptors in the rat frontal cortex (37). Therefore, it is unlikely that a depletion of 5-HT alone could account for the up-regulation of 5-HT receptors. It is possible that a combination of lower serotonergic, noradrenergic, and dopaminergic activity may account for the up-regulation of 5-HT₂ receptors.

To further explore the possibility that lower presynaptic serotonergic activity might be a cause of the greater density of 5-HT₂ receptors, we examined the relationship between imipramine binding sites and 5-HT₂ sites. Imipramine binding may be a measure of 5-HT uptake sites in serotonergic terminals. Lower imipramine binding has been reported in the brains of suicide victims in some studies (26, 27) but not others (21, 28); one study (29) reported greater [³H]imipramine binding. We also did not find any difference in the number of desipramine-sensitive B_{max} of [³H]imipramine binding sites between control subjects and suicide victims (work in preparation). However, it has been reported that desipramine-sensitive [³H]imipramine binding sites in the brain are heterogeneous (46–48) and include a significant proportion of nonspecific binding not related to the 5-HT uptake mechanism (49, 50). Hence, the binding data reported in the studies just mentioned did not adequately quantify the [³H]imipramine binding sites linked to 5-HT uptake sites. We did not find any correlations between the K_d and B_{max} of desipramine-sensitive imipramine binding and [³H]spiperone binding in control subjects (for K_d , $\rho=0.149$, $N=27$, $p=0.46$; for B_{max} , $\rho=-0.0055$, $N=27$, $p=0.98$) or suicide victims (for K_d , $\rho=0.085$, $N=26$, $p=0.68$; for B_{max} , $\rho=0.029$, $N=26$, $p=0.89$). However, because of the problems with available data on postmortem brain imipramine binding in suicide victims, the absence of a difference in imipramine binding does not necessarily preclude less serotonergic innervation in this sample. Furthermore, it is possible that there might be a diminished release of 5-HT despite a normal complement of 5-HT uptake and imipramine binding sites. It is also possible that the higher 5-HT₂ binding could be secondary to other neurochemical abnormalities in the brain, such as neuropeptidergic or neuroendocrine abnormalities, or chronobiological disturbances. It is beyond the scope of this paper to discuss these possibilities.

In summary, our results indicate that there is greater 5-HT₂ binding, evidenced by higher B_{max} , in the brains of suicide victims who used violent means of self-destruction. Since suicide victims often suffer from depression, it may be that the greater 5-HT₂ B_{max} is a way of compensating for diminished serotonergic and other monoaminergic activity in depression (the classical monoamine hypothesis of depression). Further studies are needed to determine whether the greater 5-HT₂ binding in the frontal cortex is present in patients with current or previous major depression who died of natural causes.

REFERENCES

1. Asberg M, Traskman L, Thoren P: 5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor? *Arch Gen Psychiatry* 1976; 33:1193-1197
2. Asberg M, Schalling D, Traskman-Bendz L, et al: Psychobiology of suicide, impulsivity, and related phenomena, in *Psychopharmacology: The Third Generation of Progress*. Edited by Meltzer HY. New York, Raven Press, 1987
3. Brown GL, Goodwin FK, Ballenger JC, et al: Aggression in humans correlates with cerebrospinal fluid amine metabolites. *Psychiatry Res* 1979; 1:131-139
4. Brown GL, Ebert MH, Goyer PF, et al: Aggression, suicide, and serotonin: relationships to CSF amine metabolites. *Am J Psychiatry* 1982; 139:741-746
5. Traskman L, Asberg M, Bertilsson L, et al: Monoamine metabolites in cerebrospinal fluid and suicidal behavior. *Arch Gen Psychiatry* 1981; 38:631-636
6. van Praag HM: Depression, suicide and the metabolism of serotonin in the brain. *J Affective Disord* 1982; 4:275-290
7. van Praag HM: CSF 5-HIAA and suicide in nondepressed schizophrenics. *Lancet* 1983; 2:977-978
8. Ninan PT, van Kammen DP, Scheinin M, et al: CSF 5-hydroxyindoleacetic acid levels in suicidal schizophrenic patients. *Am J Psychiatry* 1984; 141:566-569
9. Lopez-Ibor JJ Jr, Saiz-Ruiz J, Perez de los Cobos JC: Biological correlations of suicide and aggressivity in major depression (with melancholia): 5-hydroxyindoleacetic acid and cortisol in cerebral spinal fluid, dexamethasone suppression test and therapeutic response to 5-hydroxytryptophan. *Neuropsychobiology* 1985; 14:67-74
10. Roy A, Pickar D, Linnoila M, et al: Cerebrospinal fluid monoamine and monoamine metabolite levels and the dexamethasone suppression test in depression. *Arch Gen Psychiatry* 1986; 43:356-360
11. Roy-Byrne P, Post RM, Rubinow M, et al: CSF 5-HIAA and personal and family history of suicide in affectively ill patients: a negative study. *Psychiatry Res* 1983; 10:263-274
12. Virkkunen A, Nuutela A, Goodwin FK: Cerebrospinal fluid monoamine metabolite levels in male arsonists. *Arch Gen Psychiatry* 1987; 44:241-247
13. Shaw DM, Camps FE, Eccleston EG: 5-Hydroxytryptamine in the hind brain of depressive suicides. *Br J Psychiatry* 1967; 113:1407-1411
14. Pare CMB, Yeung DPH, Price K, et al: 5-Hydroxytryptamine, noradrenaline and dopamine in brain stem, hypothalamus and caudate nucleus of controls and of patients committing suicide by coal gas poisoning. *Lancet* 1969; 2:133-135
15. Lloyd KE, Fraley IJ, Deck JHN, et al: Serotonin and 5-hydroxyindoleacetic acid in discrete areas of the brain-stem of suicide victims and control patients. *Adv Biochem Psychopharmacol* 1974; 2:387-397
16. Bourne HR, Bunney WE Jr, Colburn RW, et al: Noradrenaline, 5-hydroxytryptamine, and 5-hydroxyindoleacetic acid in hind-brains of suicidal patients. *Lancet* 1968; 2:805-808
17. Beskow J, Gottfries CG, Roos BE, et al: Determination of monoamine and monoamine metabolites in the human brain: post-mortem studies in a group of suicides and a control group. *Acta Psychiatr Scand* 1976; 53:7-20
18. Cochran E, Robins E, Grote S: Regional serotonin levels in brain: a comparison of depressive suicides and alcoholic suicides with controls. *Biol Psychiatry* 1976; 11:283-294
19. Owen F, Cross AJ, Crow TJ, et al: Brain 5-HT₂ receptors and suicide. *Lancet* 1983; 2:1256-1257
20. Stanley M, McIntyre I, Gershon S: Postmortem serotonin metabolism in suicide victims, in *Abstracts of the 22nd Annual Meeting of the American College of Neuropsychopharmacology*. Nashville, ACN, 1983
21. Crow TJ, Cross AJ, Cooper SJ, et al: Neurotransmitter receptors and monoamine metabolites in the brains of patients with Alzheimer-type dementia and depression, and suicides. *Neuropharmacology* 1984; 23:1561-1569
22. Arato M, Tekes K, Tothfalusi L, et al: Serotonergic split brain and suicide. *Psychiatry Res* 1987; 21:355-356
23. Korpi ER, Kleinman JE, Goodman SI, et al: Serotonin and 5-hydroxyindoleacetic acid in brain of suicide victims: comparison in chronic schizophrenic patients with suicide as a cause of death. *Arch Gen Psychiatry* 1986; 43:594-600
24. Langer SZ, Moret C, Raisman R, et al: High affinity [³H]imipramine binding in rat hypothalamus is associated with the uptake of serotonin but not norepinephrine. *Science* 1980; 210:1133-1135
25. Paul SM, Rehani M, Skolnick P, et al: Depressed patients have decreased binding of tritiated imipramine to platelet serotonin transporter. *Arch Gen Psychiatry* 1981; 38:1315-1317
26. Stanley M, Virgilio J, Gershon S: Tritiated imipramine binding sites are decreased in the frontal cortex of suicides. *Science* 1982; 216:1337-1339
27. Paul SM, Rehani M, Skolnick P, et al: High affinity binding of antidepressants to a biogenic amine transport site in human brain and platelet: studies in depression, in *Neurobiology of Mood Disorders*. Edited by Post RM, Ballenger JC. Baltimore, Williams & Wilkins, 1984
28. Owen FJ, Chambers DR, Cooper SJ, et al: Serotonergic mechanisms in brains of suicide victims. *Brain Res* 1986; 362:185-188
29. Meyerson LR, Wennogle LP, Abel MS, et al: Human brain receptor alterations in suicide victims. *Pharmacol Biochem Behav* 1982; 17:159-163
30. Mann JJ, Stanley M, McBride A, et al: Increased serotonin₂ and β -adrenergic receptor binding in the frontal cortices of suicide victims. *Arch Gen Psychiatry* 1986; 43:954-959
31. Stanley M, Mann JJ: Increased serotonin-2 binding sites in frontal cortex of suicide victims. *Lancet* 1983; 1:214-216
32. McKeith IG, Marshall EF, Ferrier IN, et al: 5-HT receptor binding in postmortem brain from patients with affective disorder. *J Affective Disord* 1987; 13:67-74
33. Creese I, Snyder SH: [³H]-Spiroperidol labels serotonin receptors in rat cerebral cortex and hippocampus. *Eur J Pharmacol* 1978; 49:201-202
34. Lowry OH, Rosebrough NJ, Farr AL, et al: Protein measurement with the folin phenol reagent. *J Biol Chem* 1951; 193:265-275
35. van Nueten JM, Janssen PAJ, van Beek J, et al: Vascular effects of ketanserin (R-41468), a novel antagonist of 5-HT₂ serotonergic receptors. *J Pharmacol Exp Ther* 1981; 218:217-230
36. Leysen JE, Niemegeers CJE, van Nueten JM, et al: [³H]-Ketanserin (R-41468), a selective [³H]ligand for serotonin₂ receptor binding sites. *Mol Pharmacol* 1982; 21:301-314
37. Stockmeier CA, Kellar KJ: *In vivo* regulation of the serotonin-2 receptor in rat brain. *Life Sci* 1986; 38:117-127
38. Andorn AC, Huang EH, Warren AE: Specific [³H]-spiroperidol binding sites in human prefrontal cortex: potential site multiplicity and overall serotonin-like selectivity. *Life Sci* 1984; 34:2461-2466
39. DeKeyser J, LeBacker JP, Ebinger G, et al: Regional distribution of the dopamine D₂ receptors in the mesotelencephalic dopamine neuron system of human brain. *J Neurol Sci* 1985; 71:119-127

40. Chivers J, Jenner P, Marsden CD: Pharmacological characterization of binding sites identified in rat brain following *in vivo* administration of [³H]-spiperone. *Br J Pharmacol* 1987; 90: 467-478
41. Biegon A, Kargman S, Snyder L, et al: Characterization and localization of serotonin receptors in human brain postmortem. *Brain Res* 1986; 353:91-98
42. Marcusson JO, Morgan DG, Winblad B, et al: Serotonin-2 binding sites in human frontal cortex and hippocampus: selective loss of 5-HT_{2A} sites with age. *Brain Res* 1984; 311:51-56
43. Peroutka SJ, Snyder SH: Long-term antidepressant treatment decreases spiroperidol-labelled serotonin receptor binding. *Science* 1980; 210:88-90
44. Vetulani J, Lebrecht U, Pilc A: Enhancement of responsiveness of the central serotonergic system and serotonin-2 receptor density in rat frontal cortex by electroconvulsive treatment. *Eur J Pharmacol* 1981; 76:81-85
45. Biegon A, Israeli M: Quantitative autoradiographic analysis of the effects of electroconvulsive shock on serotonin-2 receptors in male and female rats. *J Neurochem* 1987; 48:1386-1391
46. Reith MEA, Sershen H, Allen D, et al: High- and low-affinity binding of [³H]imipramine in the mouse cerebral cortex. *J Neurochem* 1983; 40:389-395
47. Hrdina PD: Differentiation of two components of specific [³H]imipramine binding in rat brain. *Eur J Pharmacol* 1984; 102:481-488
48. Conway PG, Brunswick DJ: High- and low-affinity binding components for [³H]imipramine in rat cerebral cortex. *J Neurochem* 1985; 45:206-209
49. Marcusson J, Fowler CJ, Hall H, et al: "Specific" binding of [³H]imipramine to protease-sensitive and protease-resistant sites. *J Neurochem* 1985; 44:705-711
50. Marcusson J, Backstrom IT, Ross SB: Single-site model of the neuronal 5-hydroxytryptamine uptake and imipramine-binding sites. *Mol Pharmacol* 1986; 30:121-128

HIV-Related Symptoms and Psychological Functioning in a Cohort of Homosexual Men

David G. Ostrow, M.D., Ph.D., Andrew Monjan, Ph.D., Jill Joseph, Ph.D.,
Mark VanRaden, M.A., Robin Fox, M.S., Lawrence Kingsley, Dr.P.H.,
Janice Dudley, M.P.H., and John Phair, M.D.

The authors administered the Center for Epidemiological Studies Depression (CES-D) Scale to 4,954 homosexual men in the Multicenter AIDS Cohort Study. HIV antibody status at enrollment was a less important predictor of psychological distress than were reported physical symptoms. Multivariate analysis showed an association between a high score on each CES-D Scale component and the number of self-reported possible AIDS- or HIV-related symptoms, perceived lymphadenopathy, and absence of "someone to talk to about serious problems." This relationship between self-reported physical symptoms and psychological distress suggests a possible etiologic relationship between perceived AIDS risk and psychological symptoms in men at risk of AIDS.

(Am J Psychiatry 1989; 146:737-742)

The acquired immune deficiency syndrome (AIDS), first reported in 1981 (1, 2), has already had enormous psychological and social impact both on groups at high risk (3-5) and on the general public (6, 7). The discovery of a retrovirus capable of initiating the process leading to AIDS (8-10) and the development of serological tests for exposure to the human immunodeficiency virus-type I (HIV) (11, 12) have accelerated research into the natural history and broad spectrum of clinical manifestations of infection with the agent. Still, many important issues remain to be addressed, including an understanding of the factors predisposing infected individuals to develop AIDS or other HIV-related conditions and the development of therapies capable of preventing such outcomes. The incomplete state of our current knowledge regarding the natural history of HIV-related disease suggests that individuals in high-risk groups, such as homosexually active men, may experience a chronic state of concern about psych-

ical and emotional symptoms that might be prodromal to AIDS. The nonspecific nature of those symptoms (e.g., weight loss, diarrhea, fevers, rashes, cough, forgetfulness, troubled sleep, and poor concentration) compounds the difficulty experienced in attempts to cope with the ever-present risk of AIDS. The serological test for exposure to HIV, rather than resolving these uncertainties, often contributes to them because of its lack of prognostic information (13) and the threat of economic, social, or other forms of discrimination faced by seropositive individuals (14, 15). Given the multiple sources of chronic stress experienced by persons who view themselves as being at high risk of developing AIDS, it is not surprising that psychiatric researchers and clinicians are reporting a broad spectrum of psychological dysfunction in some homosexually active men (3, 4, 16-20).

To delineate more fully the epidemiology and natural history of AIDS and the full spectrum of HIV-related outcomes, the National Institutes of Health initiated the Multicenter AIDS Cohort Study (MACS), which involves approximately 5,000 homosexually active men residing in four U.S. metropolitan areas (Chicago, Baltimore/Washington, D.C., Pittsburgh, and Los Angeles). Since April 1984, 1,000 to 1,600 volunteers in each of these cities have undergone semiannual physical, immunological, and epidemiological evaluations, which have been described elsewhere (21, 22). Because of our interest in the psychological functioning of the study participants and the ultimate issue of whether or not psychological factors are important to the clinical outcome of HIV infection, we have included a brief self-report screening measure of depressive symptoms, the Center for Epidemiological Studies Depression (CES-D) Scale (23), in the MACS evaluations. This report contains the results of an exploratory cross-sectional analysis of possible relationships between CES-D Scale scores and perceived and objectively measured indicators of risk of developing AIDS at the time of enrollment in the MACS and before the men were aware of their HIV status. Other factors that might either contribute to or protect men from depression, or serve as markers for underlying psychiatric illness, were examined as well.

Received Sept. 28, 1987; revision received Dec. 1, 1988; accepted Dec. 23, 1988. From the Multicenter AIDS Cohort Study. Address reprint requests to Dr. Ostrow, Midwest AIDS Biobehavioral Research Center, ISR 2213, University of Michigan, Ann Arbor, MI 48109.

METHOD

Subjects

The subjects were 4,954 homosexual or bisexual men who volunteered for enrollment into the MACS at the four clinical study sites between April 1984 and April 1985. The total numbers included in the analyses differ because of missing or incomplete data on some measures. The men were recruited primarily through clinics, social organizations, newspaper advertisements, and word-of-mouth in the gay community. The study sample, therefore, cannot be considered as representative of the diverse population of homosexually identified men. Rather, their demographic variables are similar to those of other homosexually active men who see themselves as being at relatively high risk for development of AIDS (22).

Although men who met the Centers for Disease Control criteria for AIDS were excluded, 38% of the cohort was found to be seropositive for HIV exposure at entry into the study (21). All participants completed oral and written consent procedures, which included basic information about AIDS, "safer sex," and the risks of participating in the study. The confidentiality of all information gathered in the study is protected by a Public Health Service certificate of confidentiality, review by local and Public Health Service internal review boards, and stringent study confidentiality procedures.

Measures

The survey instruments included a self-completed sociodemographic questionnaire, an interviewer-administered physical health and epidemiological questionnaire, and a standardized physical examination. Questions about both licit and illicit drug use during the past 2 years, the past 6 months, and the past 7 days were extensive and have been detailed elsewhere (21, 22). Each subject completed the CES-D Scale and several additional psychosocial screening questions regarding his general sense of well-being and the number of persons with whom he could discuss personal problems. This questionnaire was completed before the physical examination in all cases, and in most cases before the health/risk factor interview as well.

The CES-D Scale form used was directly adapted from the instrument developed by Radloff (23). The subject recorded the frequency of each psychological symptom during the past week by assigning a value of 0–3 to indicate "rarely or none of the time (<1 day per week)," "some or little of the time (1–2 days per week)," "occasionally or moderate amount of the time (3–4 days per week)," and "most or all of the time (5–7 days per week)." A total score and scores on the four subscales (depression, enervation, negative affect, and interpersonal sensitivity) were derived, as described by Ross and Mirowsky (24). The positively worded items were reversed, and the 20 item scores were summed. Thus, the range of possible scores was 0

to 60. A cutoff score of 16 or more, corresponding to the 80th percentile in large-scale community surveys (25), has been used in previous urban samples to designate probable cases of clinical depression (26). The scores of the married men in the study by Ross and Mirowsky (24) were used as references in this study.

The men in our cohort were asked to indicate their sexual orientation during the past 5 years according to the commonly used self-report version of the seven-category Kinsey scale. Ross and Mirowsky (24) did not indicate the Kinsey scale status of the married men in their study, and we did not inquire as to the marital status of our study participants.

HIV antibody status was determined by means of DuPont ELISA (12). Self-reported possible HIV symptoms were elicited as part of the physical health/epidemiology interview that took place after the CES-D Scale was completed and before the physical examination. The symptoms assessed were as follows: swollen lymph glands; sore mouth or throat; new skin rash; persistent fatigue; diarrhea; persistence or recurrence of temperature higher than 100 °F; night sweats; persistent, frequent, or unusual headaches; muscle or joint pains; persistent shortness of breath; new or unusual dry cough; thrush, candida, or white patches in the mouth or throat; unusual bruise, bump, or skin discoloration; and unintentional weight loss of at least 10 lb. Any that had been present during the past 6 months and had lasted 2 weeks or longer was recorded as present. In the statistical analyses, swollen lymph glands were analyzed separately and therefore not included in the symptom factor.

Statistical Analysis

Potential risk factors were initially screened for evidence of association with scores on the total CES-D Scale and its four component subscales by means of conventional univariate methods. Factors measured on continuous scales were grouped into approximately four intervals. All factors were then subjected to one-way analyses of variance (ANOVAs) against the total CES-D Scale score and the subscores. The cell means were examined to ensure that nonsignificance of ANOVA F test results was not caused by systematic (e.g., linear or quadratic) effects. Differences between study sites were tested with two-tailed t tests and the Bonferroni correction to adjust for multiple pairwise comparisons.

Multivariate analyses employed the BMDPLR multiple logistic regression model. For the logistic analysis, total CES-D Scale scores of 16 or more were classified as high. The cutoffs used to classify the subscores as high were directly proportional to the cutoff for the total score; the frequency of high values was greater for the subscores than for the total score, however, since one or more high subscores could be balanced by lower than average values in other subscores.

Each factor whose association with a CES-D Scale component had a univariate p value of less than 0.05 was considered for entry into the model for that com-

TABLE 1. CES-D Scale Scores and Prevalence of Self-Reported HIV-Related Symptoms in Homosexual Men Tested for HIV Antibodies and CES-D Scale Scores for a Reference Sample

Group	CES-D Scale Score										Prevalence of Self-Reported HIV-Related Symptoms (%) ^a		
	Depression		Enervation		Negative Affect		Inter-personal Sensitivity		Total		One Symptom	Two Symptoms	Three Symptoms
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Homosexual men	3.26	3.6	3.28	3.1	2.71	3.0	0.47	0.9	9.77	8.9	41	18	9
HIV-negative (N=2,875)	3.17 ^b	3.5	3.15 ^c	3.0	2.72	3.1	0.46	0.9	9.54 ^d	8.9	35	14	7
HIV-positive (N=1,775)	3.40 ^b	3.6	3.49 ^c	3.2	2.70	3.0	0.48	0.9	10.14 ^d	8.9	50	24	13
Married men studied previously (N=680)(24)	1.96	3.1	3.48	3.5	2.96	3.0	0.48	1.2	8.88	7.5	—	—	—

^aSee text for list of symptoms.^bF=4.81, df=1, 4648, p=0.028.^cF=13.67, df=1, 4648, p=0.0002.^dF=5.10, df=1, 4648, p=0.024.

ponent. The stepwise forward approach was used to select the variables for the final models. Each variable whose partial F statistic had a p value of less than 0.01 was included in the models presented. Each of the coefficient estimates produced in the modeling was exponentiated to obtain the estimated odds of a high score, adjusted for the effects of all other variables in the model. The overall significance of each model was assessed by means of the likelihood ratio chi-square statistic (27).

RESULTS

The total CES-D Scale scores and subscale scores of the MACS subjects, stratified by HIV serological status, are shown in table 1. Also shown are the CES-D data on the married men described by Ross and Mirowsky (24) and the proportion of MACS men reporting one or more possible HIV-related symptoms. The mean score on the CES-D Scale depression subscale for the entire MACS cohort was more than one point higher than the score for the married men, and there was a smaller difference in the total score. The seronegative and seropositive MACS participants differed significantly on the total score and on two of the four subscale scores, but none of these differences was clinically significant. Substantial proportions of both the seropositive and seronegative homosexual men reported having one or more possible HIV-related physical symptoms in the last 6 months (table 1).

When univariate techniques were used to screen the relationship of several factors to CES-D Scale scores in the MACS cohort, many associations were observed (table 2). The subjects reporting a substantially bisexual orientation (Kinsey score=3–6) had higher mean CES-D Scale scores than those endorsing an "exclusively homosexual" orientation. Younger subjects and those with lower socioeconomic status also reported more symptoms. Men who reported use of marijuana, volatile nitrites ("poppers"), cocaine, methylenedioxymphetamine (MDA), or phencyclidine (PCP) had

somewhat higher scores on the enervation subscale. Use of downers or opiates was correlated with high scores on all CES-D Scale subscales except negative affect. Respondents who reported receptive anal intercourse with most or all sex partners during the past 2 years had high scores on the CES-D Scale depression and enervation subscales. The subjects who were uncertain whether they had had sexual exposure to someone who later developed AIDS had high depression and enervation scores, while the scores of the subjects who reported definite sexual contact with partners who developed AIDS had scores intermediate between those of the men who were uncertain and the men who did not have such contact.

The men who reported the absence of confidants (persons they could "talk to about serious problems") had higher scores on each CES-D Scale subscale and the total CES-D Scale than men who had such support. The mean subscale and total scores of the men who reported more than three possible HIV-related symptoms were twice as high as the scores of those not reporting any symptoms. Persons reporting swollen glands had significantly higher scores on the depression, enervation, and negative affect subscales and on the total CES-D Scale, whether or not enlarged lymph nodes were detected at the physical examination performed immediately after the health interview. Regarding use of prescribed psychotropic medication during the last 6 months, 15 men (0.3%) reported they had used lithium, 206 (4.2%) reported antidepressant use, and 875 (17.8%) reported the use of sedative/hypnotics or tranquilizers. Use of any of these three classes of psychotropic medication was associated with higher CES-D Scale scores according to univariate analysis.

We performed a multiple logistic regression analysis to examine the relationship of each significant univariate factor to the CES-D Scale subscale and total scores. Since data on prior psychiatric hospitalization, suicide attempts, psychotherapy, and family history of psychiatric illness were unavailable for this cohort, history of psychotropic drug use served as a marker for

TABLE 2. Significant Univariate Associations With CES-D Scale Scores in 4,648 Homosexual Men

Variable ^a	Direction of Score				Total
	Depression Subscale	Enervation Subscale	Negative Affect Subscale	Interpersonal Sensitivity Subscale	
Bisexuality (Kinsey score=3-6)	↑		↑		↑
Age	↓	↓		↓	↓
Occupational status	↓	↓	↓	↓	↓
Educational level	↓	↓	↓	↓	↓
Black			↑		
Residence in Los Angeles	↑	↑		↑	↑
Residence in Pittsburgh			↑		↑
More than 50 sexual partners in last 2 years		↑		↑	↑
Receptive anal sex with most partners	↑	↑			↑
Anonymous sex partners	↑	↑	↑	↑	↑
Use of psychotropic drugs in last 6 months					
Tranquilizers, mood elevators, or lithium	↑	↑	↑	↑	↑
Marijuana or PCP		↑			
"Poppers," cocaine, or MDA		↑	↓		
"Downers" or opiates	↑	↑		↑	↑
"Uppers"		↑			↑
Intravenous drug use ever ^b	↑	↑			↑
HIV antibody seropositivity	↑	↑			↑
Reported enlarged glands	↑	↑	↑		↑
Sex with person with possible or definite AIDS	↑	↑			↑
No one to talk to	↑	↑	↑	↑	↑
Number of possible HIV-related symptoms in last 6 months ^c	↑	↑	↑	↑	↑

^aSignificantly associated with score on at least one CES-D subscale or on total scale, according to ANOVA ($p < 0.05$).

^bMen who reported any drug use in the past 2 years were asked if they had ever used drugs intravenously.

^cSee text for list of symptoms.

prior affective disturbance (lithium or antidepressant use) or other psychiatric problems (tranquilizers or sedative/hypnotic use). As shown in table 3, a pattern was observed across the various CES-D Scale factors; the number of self-reported HIV-related symptoms and the absence of "someone to talk to about serious problems" were consistently associated with high CES-D Scale total and subscale scores. Although perception of swollen lymph nodes was important, its documentation during physical examination was not. HIV seropositivity significantly attenuated the association of perceived gland enlargement with high CES-D Scale scores. On multiple logistic regression analysis, none of the previously observed associations between recreational drug use and high CES-D Scale scores was present; cocaine was mildly associated with low negative affect scores. In all, nine different factors were found to have significant independent associations with high scores on the total CES-D Scale score or one or more subscales. For all but two of these factors, adjusted odds ratios in excess of 2.0 were found.

DISCUSSION

The findings reported here clearly indicate that self-reported HIV-related symptoms—such as swollen

glands, weight loss, and fever—are associated with higher psychological symptom scores in a cohort of homosexual/bisexual men, regardless of HIV antibody status, examiner-verified lymphadenopathy, or recent use of psychotropic medications. The effect of perceived physical symptoms on psychological functioning may add to the distress of persons with inadequate social support networks. The possible alternative explanations that men prone to depression are more cognizant of bodily symptoms or that they may withdraw from or misperceive the availability of social support need to be considered. Prospective research in this population may help to clarify the actual reasons for more depressive symptoms in men with self-perceived HIV symptoms and inadequate perceived social support.

The cohort examined in this study sees itself, and indeed is, at high risk of developing an incurable and fatal syndrome (28). Although a significant proportion of these men may not develop AIDS, at the time of their enrollment and baseline CES-D Scale data collection none knew whether or not he had been infected with HIV. Whether we focus on the group that failed to report the presence of lymph nodes which were palpable on examination or the group that reported swollen glands which were not demonstrable on examination, the reciprocal effects of denial and somatization

TABLE 3. Multiple Logistic Regression Analysis of Association Between Significant Univariate Factors and High CES-D Scale Scores^a in Homosexual Men

Factor ^b	N ^c	Adjusted Relative Odds Ratio ^d				
		Depression	Enervation	Negative Affect	Interpersonal Sensitivity	Total
Number of reported possible HIV-related symptoms ^e						
0 or 1	3,888	1.00	1.00	1.00	1.00	1.00
2 or 3	513	2.30	3.01	1.89	1.51	2.50
≥4	173	4.24	7.51	2.58	2.19	5.11
Use of psychotropic drugs						
None	3,665	1.00	1.00	1.00	1.00	1.00
Hypnotics	720	1.76	1.48	1.52	1.44	1.94
Antidepressants or tranquilizers	89	3.69	3.07	3.43	2.20	4.98
Both hypnotics and antidepressants or tranquilizers	100	3.73	3.71	1.99	2.27	3.31
No one to talk to	175	3.68	2.76	3.94	2.35	3.58
Reported enlarged glands						
HIV-positive						
No	2,716	1.00	1.00	1.00		1.00
Yes	118	2.87	1.35	2.30		3.17
HIV-negative						
No	1,444	0.91	0.99	0.96		0.98
Yes	296	1.40	1.56	1.19		1.29
Age (years)						
≥45	363	1.00	1.00		1.00	1.00
25-44	3,706	1.45	1.31		1.72	1.41
<25	505	1.93	2.18		2.69	1.98
Education						
Graduate school	1,592		1.00	1.00	1.00	1.00
College	2,399		1.32	1.29	1.45	1.31
High school	583		1.28	2.02	1.68	1.74
Anonymous sex partners	2,625	1.26	1.22	1.22	1.37	
Did not use cocaine	3,005			1.34		
Possibly or definitely had sex with a man with current or subsequent AIDS	932	1.29				

^aHigh score defined as 16 or higher.^bAll history variables pertain to the 6 months before entry into the study. Only factors whose partial F test p values were less than 0.01 were included in a model. The factors are listed in descending order according to their largest relative odds among all models (i.e., for total score and for subscores).^cThe numbers of subjects given are minimum values. The total for each model (≥4,574) was determined by the number of cases that had complete data for all the included variables.^dThe overall significance of each model was as follows: depression— $\chi^2=458.5$, $df=13$, $p<0.0001$; enervation— $\chi^2=519.1$, $df=14$, $p<0.0001$; negative affect— $\chi^2=342.5$, $df=13$, $p<0.0001$; interpersonal sensitivity— $\chi^2=154.1$, $df=11$, $p<0.0001$; total— $\chi^2=473.8$, $df=13$, $p<0.0001$.^eSee text for list of symptoms.

are important in explaining why some men at risk of AIDS experience depressive symptoms. That greater age and education level were associated with less psychological distress in this cohort is consistent with the psychosomatic literature.

The observed relationship between perception of HIV-related symptoms and psychological distress is further complicated by the nonspecificity of those symptoms and their overlap with symptoms used to assess depression, anxiety, and enervation levels (3, 4, 20). We were careful to focus our attention on symptoms, such as swollen glands, that are not directly assessed by the CES-D Scale and for which we had both self- and observer ratings. Other possible HIV-related symptoms, however, such as difficulty in concentrating, sleep disturbance, fatigue, and poor appetite, are nonspecific and may contribute to high CES-D Scale scores. Thus, it is important to look at relatively spe-

cific symptoms when assessing the relationship between physical and mental health in persons at high risk of HIV infection.

The finding that HIV seropositivity was not independently associated with high CES-D Scale scores, and that seropositive men with swollen glands actually scored lower than their seronegative counterparts on several subscales, argues strongly against a major role of occult early-stage HIV infection in the observed relationship between perceived HIV-related symptoms and the high psychological symptom scores reported here. Furthermore, the rate of conversion from negative to positive HIV antibody status in the following 6 months among seronegative men who reported the presence of enlarged glands at entry was no different from the rate for men who did not report swollen glands (2.4% versus 3.6%, respectively). This argues against the possibility that the high CES-D Scale scores

seen in seronegative men who reported swollen glands were due to undetected early-stage HIV infection.

Self-report of HIV-related symptoms, rather than observer-verified symptoms or HIV serological status, appears to be the primary factor associated with the abnormally high depressive symptom scores in this cohort. The magnitude of the association between self-reported HIV-related symptoms and high CES-D Scale scores, as judged by their odds ratios, is considerable and not attenuated by HIV serological status, recent psychotropic drug use, or other factors. Further, the finding that HIV-negative individuals were just as likely as seropositive subjects to endorse such enervation scale items as "difficulty concentrating," "everything an effort," and "talked less" cautions us to be skeptical of suggestions that subtle cognitive symptoms should automatically be attributed to CNS HIV infection in a person at high risk of HIV infection. Ongoing studies using observer-rated tests of cognitive function in carefully matched HIV-positive and HIV-negative cohorts may be informative in this regard (29).

ACKNOWLEDGMENT

The principal investigators and co-investigators in the Multicenter AIDS Cohort Study (MACS) were as follows: Johns Hopkins University School of Hygiene and Public Health, Baltimore—B. Frank Polk, M.D., M.Sc., Robin Fox, M.S., Homayoon Farzedegan, Ph.D., Alvaro Munoz, Ph.D., Joseph Margolick, M.D., Ph.D., Alfred J. Saah, M.D., M.P.H.; Howard Brown Memorial Clinic—Northwestern University Medical School, Chicago—John P. Phair, M.D., Joan S. Chmiel, Ph.D., David G. Ostrow, M.D., Ph.D.; University of California, Los Angeles—Roger Detels, M.D., M.S., Barbara R. Visscher, M.D., Dr.P.H., John L. Fahey, M.D., M.S., Janis V. Giorgi, Ph.D., Jan Dudley, M.P.H.; University of Pittsburgh Graduate School of Public Health and School of Medicine—Charles R. Rinaldo, Jr., Ph.D., Monto Ho, M.D., Lawrence A. Kingsley, Dr.P.H., David W. Lyter, M.D., Ronald O. Valdiserri, M.D., Alan Winkelstein, M.D., James Becker, Ph.D.; National Institute of Allergy and Infectious Diseases, Bethesda, Md.—Richard A. Kaslow, M.D., M.P.H., Jack Killen, M.D., Mark J. VanRaden, M.A.; National Cancer Institute, Bethesda, Md.—Andrew A. Monjan, Ph.D., M.P.H., Iris Abrams, M.D. The investigators at the MACS data coordinating center at the Johns Hopkins School of Hygiene and Public Health were Alvaro Munoz, Ph.D., V. Cary, L.P. Jacobsen, K.Y. King, C. Meinait, S. Su, M.C. Wang, and S. Zeger.

REFERENCES

- Centers for Disease Control: *Pneumocystis pneumonia*—Los Angeles. MMWR 1981; 30:250–252
- Centers for Disease Control: Kaposi's sarcoma and pneumocystis pneumonia among homosexual men—New York City and California. MMWR 1981; 30:305–308
- Ostrow DG: Psychiatric consequences of AIDS: an overview. *Int Rev Neurosci* 1986; 29:1–13
- Holland JC, Tross S: The psychosocial and neuropsychiatric sequelae of AIDS and related disorders. *Ann Intern Med* 1985; 103:760–764
- Coats TJ, Stall R, Mendell JS, et al: AIDS: a psychosocial research agenda. *Ann Behav Med* 1987; 9:21–28
- Ostrow DG: Medical responses to AIDS, in *Psychiatric Implications of AIDS*. Edited by Nichols SE, Ostrow DG. Washington, DC, American Psychiatric Press, 1984
- Bayer R, Fox DM, Willis DP (eds): *AIDS: The Public Context of an Epidemic*. New York, Cambridge University Press, 1986
- Gallo RC, Salahuddin SZ, Popovic M, et al: Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science* 1984; 224:500–503
- Montagnier L, Cherman J, Barre-Sinoussi F, et al: A new human T-lymphotropic retrovirus: characterization and possible role in lymphadenopathy and AIDS, in *Human T Cell Leukemia Viruses*. Edited by Gallo RC, Essex M, Gross L. New York, Cold Spring Harbor Press, 1984
- Levy JA, Hoffman AD, Kramer SM, et al: Isolation of lymphocytotropic retroviruses from San Francisco patients with AIDS. *Science* 1984; 225:840–842
- Sarngadharan MG, Popovic M, Bruch L, et al: Antibodies reactive with human T-lymphotropic retroviruses (HTLV-III) in the serum of patients with AIDS. *Science* 1984; 224:506–508
- Petricianni JC: Licensed tests for antibody to human T-lymphotropic virus, type III: sensitivity and specificity. *Ann Intern Med* 1985; 103:726–729
- Ostrow DG: Medical and psychological implications of HTLV-III antibody testing. *Chicago Med* 1985; 88:474–478
- New York City Commission on Human Rights: Report of the AIDS Discrimination Unit—AIDS and People of Color: The Discriminatory Impact. New York, New York City Commission on Human Rights, 1986
- Leonard AS: Employment discrimination against persons with AIDS. *University of Dayton Law Rev* 1985; 10:681–703
- Marzuk PM, Tierney H, Tardiff K, et al: Increased risk of suicide in persons with AIDS. *JAMA* 1988; 259:1333–1337
- Perry SW, Tross S: Psychiatric problems of AIDS inpatients at the New York Hospital: preliminary report. *Public Health Rep* 1984; 99:200–205
- Ostrow DG: Psychosocial aspects of AIDS. *Masters in Psychiatry* 1985; 1:21–23
- Dilley JW: Treatment interventions and approaches to care of patients with AIDS, in *Psychiatric Implications of AIDS*. Edited by Nichols SE, Ostrow DG. Washington, DC, American Psychiatric Press, 1984
- Joseph JG, Emmons C, Kessler RC, et al: Coping with the threat of AIDS: an approach to psychosocial assessment. *Am Psychol* 1984; 39:1297–1302
- Chmiel J, Detels R, Kaslow RA, et al: Factors associated with prevalent human immunodeficiency virus (HIV) infection in the Multicenter AIDS Cohort Study. *Am J Epidemiol* 1987; 126:568–577
- Kaslow RA, Ostrow DG, Detels R, et al: The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. *Am J Epidemiol* 1987; 126:310–318
- Radloff LS: The CES-D Scale: a self-report depression scale for research in the general population. *Applied Psychol Measurement* 1977; 1:385–401
- Ross CE, Mirowsky J: Components of depressed mood in married men and women. *Am J Epidemiol* 1984; 119:997–1004
- Aneshensel CS, Frerichs RP, Clarke VA: Family roles and sex differences in depression. *J Health Soc Behav* 1981; 22:379–393
- Weissman MM, Scholomskas O, Pottenger M, et al: Assessing depressive symptoms in five psychiatric populations: a validation study. *Am J Epidemiol* 1977; 106:203–214
- Cox DR: *The Analysis of Binary Data*. New York, Chapman and Hall, 1970, p 93
- Polk BF, Fox R, Brookmeyer R, et al: Predictors of the acquired immunodeficiency syndrome developing in a cohort of seropositive homosexual men. *N Engl J Med* 1987; 316:61–66
- McArthur JC, Cohen BA, Selnes OA, et al: Low prevalence of neurological and neuropsychological abnormalities in otherwise healthy HIV-1-infected individuals: results from the Multicenter AIDS Cohort Study (abstract), in *Proceedings of the IVth International AIDS Conference*, Stockholm, Government of Sweden, 1988

TSH Response to TRH in Depression With and Without Panic Attacks

Gregory M. Gillette, M.D., James C. Garbutt, M.D., and Dana E. Quade, Ph.D.

Low thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) has been repeatedly described in approximately 25% of patients with major depression. Panic disorder appears related to depression along several dimensions, including prevalence of low TSH response to TRH. The authors divided 46 patients with primary unipolar depression by gender and by presence or absence of concurrent panic attacks and compared their TRH test results with those of 106 normal control subjects, controlling for confounding variables. Depressed patients with panic had higher prevalence of low TSH response and significantly lower mean TSH response than depressed patients without panic. The latter were indistinguishable from normal control subjects.

(Am J Psychiatry 1989; 146:743-748)

In recent years considerable interest has developed concerning the phenomenology and biology of panic disorder and its relationship to major depression. Case history (1-4), genealogic (5, 6), pharmacologic (4, 7), and physiologic studies, e.g., of plasma catecholamines (8, 9) and melatonin secretion (10, 11), all indicate a close biologic connection between panic disorder and major depression.

Low thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) has been extensively reported in patients with major depression (12, 13). Attempts to clinically characterize those depressed patients with low TSH response have been relatively uninformative, although greater depersonalization/derealization (14), agitation (14, 15), violent

suicidality (16), and duration of illness (17) have been associated with low response.

Several recent studies have reported that 33%-40% of patients with panic disorder show low TSH response to TRH (18-20). Because of our long-standing interest in the TRH test as a putative biologic marker in major depression and the conceptualization of panic and depression as expressions of a "partially shared diathesis" (5), these reports of low TSH response in panic disorder prompted us to reassess our TRH test findings by grouping depressed subjects into those with and those without concurrent panic attacks. We hypothesized that depressed patients with concurrent panic attacks would show higher prevalence of low TSH response to TRH and lower mean TSH response than those without panic attacks.

METHOD

Subjects and Clinical Methods

Subjects were studied at the Dorothea Dix Hospital Clinical Research Unit, a 16-bed adult psychiatric inpatient ward devoted to psychoendocrine research. Normal control subjects were recruited by community and university newspaper advertisement.

Patients studied in the previous 5 years who met the following criteria were included. 1) All had a Research Diagnostic Criteria (RDC) diagnosis of primary unipolar major or minor depression. 2) All had the Schedule for Affective Disorders and Schizophrenia (SADS) administered by an experienced psychiatrist or social worker. 3) All were clinically and chemically euthyroid, with normal screening thyroxine (T_4), triiodothyronine (T_3) resin uptake, free thyroxine index, and basal TSH. 4) All (except three exceptions noted later) were medically healthy according to history, physical, and screening laboratory examinations. 5) All underwent a standard TRH test after at least 1 week free of tricyclic antidepressants, 2 weeks free of monoamine oxidase inhibitors or antipsychotics, and 3 weeks free of lithium or carbamazepine. None had current alcohol abuse.

Two women with panic attacks, mitral valve prolapse, and frequent cardiac supraventricular tachyarrhythmias of necessity continued taking moderate

Presented at the 140th annual meeting of the American Psychiatric Association, Chicago, May 9-14, 1987. Received March 30, 1988; revision received Nov. 22, 1988; accepted Dec. 1, 1988. From the Clinical Research Unit, Dorothea Dix Hospital; and the Departments of Psychiatry and Biostatistics, University of North Carolina, Chapel Hill. Address reprint requests to Dr. Gillette, Clinical Research Unit, Dorothea Dix Hospital, Raleigh, NC 27611.

Supported by NIMH Mental Health Research Center grant MH-33127 and by the Foundation of Hope for Research and Treatment of Mental Illness, Raleigh, N.C.

The authors thank Bess Dew, R.N., and the Clinical Research Unit nursing staff for clinical and research support and Betty Benson for project coordination and data management.

Copyright © 1989 American Psychiatric Association.

doses of propranolol at the time of TRH testing. One woman without panic was taking low-dose conjugated estrogens/methyltestosterone for posthysterectomy/oophorectomy atrophic vaginitis previously complicated by recurrent rectovaginal fistula. Twelve of 27 women and 11 of 19 men had taken either a bedtime hypnotic (benzodiazepine, chloral hydrate) or a daytime anxiolytic (benzodiazepine, alprazolam) or both sometime during the week immediately before TRH testing.

We determined patients' RDC diagnoses at a formal conference involving medical staff, nursing staff, and ward social worker. All available past psychiatric records, current clinical observations, SADS results, scores on the Hamilton Rating Scale for Depression, and MMPI profiles were considered in determining diagnoses. The director of the clinical research unit, an experienced research psychiatrist, assigned all final diagnoses.

A critical step for achieving the major goal of the study was to divide the depressed patients into those with and those without panic attacks during their current depressive illness episode. This could not be done by reviewing diagnoses because RDC convention precluded concurrent diagnosis of panic disorder and depression. We used SADS items 251–261 to establish the presence or absence of current panic attacks. Item 251 asks about the presence of fearful attacks, and each one of items 252–261 asks about a specific physical symptom of these attacks, with at least two physical symptoms needed to designate fearful episodes as panic attacks. It should be noted that in the SADS algorithm, specific physical symptoms are asked about only if item 251 is definitively endorsed; this leaves open the possibility of false negatives for diagnosis of panic disorder if the subject responds negatively to the single screening question concerning fearful episodes, even though he or she, if asked about them, might have endorsed numerous specific symptoms. Only one of our 14 patients with panic attacks endorsed the minimum number of two symptoms to meet the RDC for diagnosis of panic disorder. The other 13 patients with panic endorsed three to six symptoms each, making false positives for panic unlikely. SADS item 262 inquires about the number of consecutive weeks with panic attacks. All of our patients with current panic attacks fell cleanly into two groups on the basis of data from this item: those with panic attacks during their depressive episode (six women and three men) and those with long-standing panic attacks that preceded their current depressive episode and continued into it (four women and one man). Our lifetime SADS data were insufficiently complete to reliably determine the prevalence of prior panic attacks in patients without current panic attacks. We also used RDC diagnoses to subtype patients into endogenous versus nonendogenous groups.

The SADS provided information about duration of current illness episode and interval since first depressive episode. We used the first 17 items of the Hamilton depression scale, administered by an experienced

research psychiatrist immediately before TRH infusion, to assess depression severity.

Forty-six patients (44 inpatients and two outpatients) met the study criteria. Forty-five had RDC major depression and one had RDC minor depression. The sample contained 27 women, with a mean \pm SD age of 38.2 ± 9.3 years, and 19 men, with a mean \pm SD age of 37.9 ± 10.4 years. Ten women (37%) and four men (21%) had current panic attacks; these figures are comparable to previously reported prevalences (3, 4). Although data from some of these patients have been previously used in other reports from our unit, these subjects have never been reported as a group.

We studied 106 medically healthy normal volunteers without current or past psychiatric illness, alcoholism, or substance abuse disorder, and no first-degree relative with psychiatric illness or alcoholism, as established by unstructured clinical screening interview. No SADS was administered to normal subjects. The volunteers consisted of 38 normal women, with a mean \pm SD age of 33.5 ± 8.9 years, and 68 normal men, with a mean \pm SD age of 32.8 ± 9.8 years.

Each patient and control subject underwent a standard TRH test after having the procedure fully explained and giving written informed consent. After fasting overnight, at 8:30 a.m., each subject had a butterfly needle inserted into a forearm vein for serial blood sampling and TRH infusion. The vein was kept open by slow normal saline drip. Blood samples for baseline measurement of TSH, cortisol, T_4 , and T_3 resin uptake were drawn at 9:00 a.m. Immediately thereafter, 500 μ g of TRH were infused over 1 minute. Blood samples for postinfusion TSH were drawn at 9:30 a.m.

Laboratory Methods

Blood was allowed to clot before the serum was separated and frozen at -20°C . All samples were assayed in duplicate, with the laboratory blind to patient diagnosis. The assay methodologies and respective intra-assay and interassay coefficients of variation were as follows: TSH, Beckman radioimmunoassay kit, 4.8% and 5.9%, respectively; prolactin, Serono radioimmunoassay kit, 3.8% and 6.1%; cortisol, Corning radioimmunoassay kit, 4.2% and 5.6%; T_4 , Becton-Dickinson radioimmunoassay kit, 5.5% and 7.0%; and T_3 resin uptake, Ames Sephadex Column separation of free [^{125}I] T_3 from that bound to serum, 4.6% and 7.3%.

In mid-1985, we changed TSH assay method to an immunoradiometric assay (Hybritech, Inc.). Because 29 of 46 patients and all normal subjects had been studied before the change, we converted Hybritech results to Beckman equivalents before data analysis, using a mathematically derived conversion factor (described later).

TABLE 1. Endocrine Values in Normal Control Subjects and Depressed Patients With and Without Panic Attacks

Measure	Normal Subjects			Depressed Patients Without Panic Attacks			Depressed Patients With Panic Attacks		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Women									
TSH (μ U/ml)									
Time 0 ^a	38	3.3	1.1	17	3.3	1.3	10	3.5	1.2
Time 30 ^{b,c}	38	18.3	8.7	17	17.4	7.2	10	12.9	4.5
Δ TSH30 ^{d,e}	38	14.9	8.4	17	14.1	6.8	10	9.4	3.8
Free thyroxine index (ng/dl) ^a	38	6.4	1.5	17	6.9	1.5	10	5.9	1.3
Serum cortisol (μ g/dl) ^a	23	14.5	7.7	17	13.3	6.0	10	15.1	5.2
Men									
TSH (μ U/ml)									
Time 0 ^a	68	3.2	1.4	15	3.4	1.2	4	3.6	0.7
Time 30 ^{b,f}	68	14.6	5.7	15	12.9	4.5	4	8.5	2.8
Δ TSH30 ^{d,g}	68	11.3	5.2	15	9.5	3.5	4	4.9	2.7
Free thyroxine index (ng/dl) ^{a,h}	66	5.9	1.6	15	7.2	1.8	4	6.7	0.8
Serum cortisol (μ g/dl) ^a	56	14.5	8.6	15	18.3	10.2	4	12.7	3.0

^aImmediately before TRH infusion.^bThirty minutes after TRH infusion.^cDepressed patients with panic attacks differed significantly from normal subjects ($t=1.94$, $df=62$, $p=0.03$) and from patients without panic attacks ($t=1.45$, $df=62$, $p=0.08$).^dValue at time 30 minus value at time 0.^eDepressed patients with panic attacks differed significantly from normal subjects ($t=2.10$, $df=62$, $p=0.02$) and from patients without panic attacks ($t=1.60$, $df=62$, $p=0.06$).^fDepressed patients with panic attacks differed significantly from normal subjects ($t=2.17$, $df=84$, $p=0.02$) and from patients without panic attacks ($t=1.43$, $df=84$, $p=0.08$).^gDepressed patients without panic attacks differed significantly from patients with panic attacks ($t=1.68$, $df=84$, $p=0.05$), and depressed patients with panic attacks differed significantly from normal subjects ($t=2.55$, $df=84$, $p=0.01$).^hDepressed patients without panic attacks differed significantly from normal subjects ($t=-2.88$, $df=82$, $p=0.01$).

Statistical Methods

Because panic disorder is a predominantly (but not exclusively) female disorder and because the study included unequal numbers of men and women for all three comparison groups, we analyzed data for each gender separately. For the 17 patients with TSH assayed by the Hybritech method (X), we applied the formula $Y=2.09+(1.42 \times X)$ to estimate the level that would have been attained with the Beckman method (Y). We had determined this formula by using least-squares linear regression of Y on X, given duplicate assays of 504 blood samples from a different group of 17 subjects.

For each line of table 1 involving TSH values, we performed an overall analysis of variance to test the hypothesis of equal means for the three groups (normal, depressed without panic, and depressed with panic) against the ordered alternative of means in the order normal > depressed without panic > depressed with panic. If this overall test was significant at $p < 0.05$, we compared the three pairs of means with one-tailed t tests. For lines not involving TSH, the procedure was similar, but the overall test was directed against general alternatives and the t tests were two-tailed.

To test whether some variable X might be confounding the association between panic attacks and low Δ TSH30, we calculated the classical partial correlation between Δ TSH30 and Panic (a dummy variable equal to 1 for patients with panic and 0 otherwise) given X; the test statistic is a t with (N minus 3) degrees of

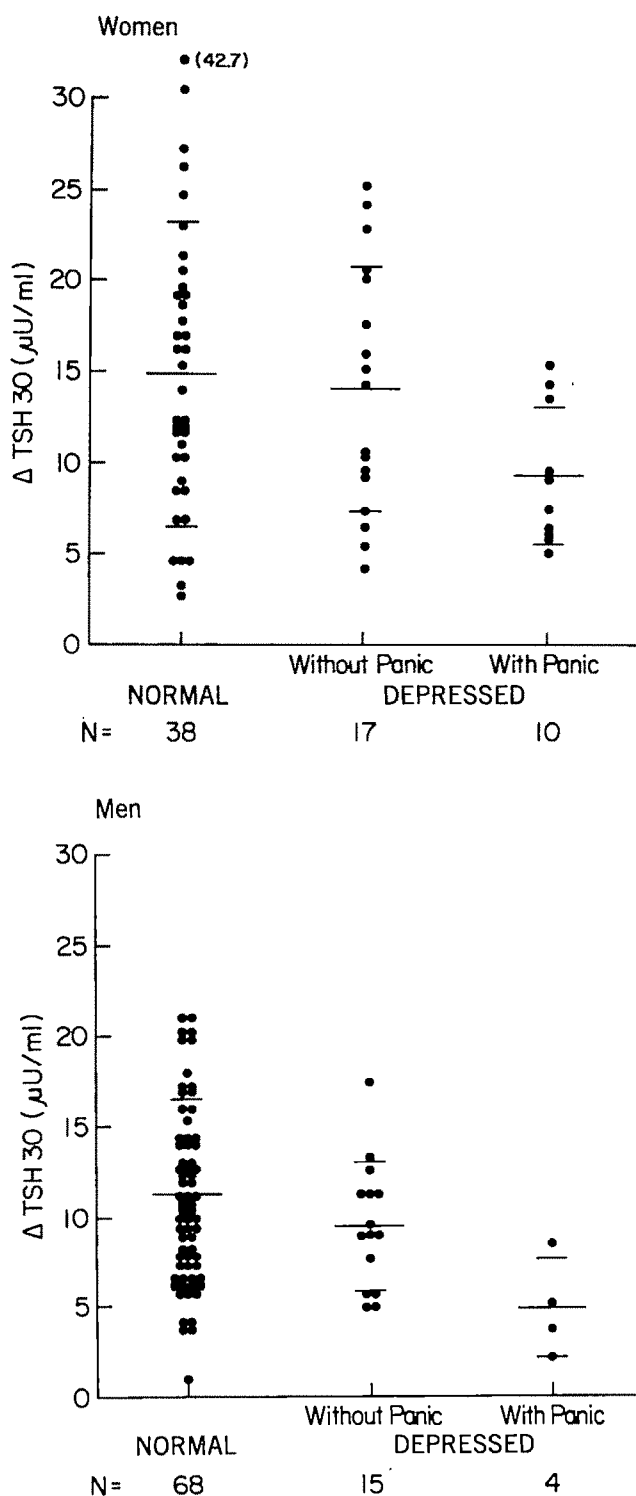
freedom. Conversely, to test whether X had any effect on Δ TSH30 beyond that explained by panic, we calculated the partial correlation between X and Panic given Δ TSH30.

We used t tests to assess the effect of recent sedative or anxiolytic ingestion on Δ TSH30. We used Fisher's exact test to determine whether Δ TSH30 was related to length of time since onset of panic attacks (only during depressive episode versus preceding and continuing into depressive episode). We used an arbitrary threshold for Δ TSH30 of 6.5 μ U/ml to dichotomize the sample of depressed women with panic for purposes of analysis. There were too few men with panic to make such analysis meaningful.

RESULTS

A summary of endocrine findings by group and gender is shown in table 1. Figure 1 shows the distribution of Δ TSH30 values in the three comparison groups by gender.

Mean Δ TSH30 values showed no significant differences between normal and depressed subjects without panic attacks (for women, $t=0.38$, $df=62$, $p=0.36$; for men, $t=1.30$, $df=84$, $p=0.10$). By contrast, mean Δ TSH30 in depressed women with panic was significantly lower than that in normal women (table 1). There was also a strong trend toward lower mean Δ TSH30 in depressed women with panic than in depressed women without panic. Results were similar for

FIGURE 1. TSH Response to TRH Among Normal and Depressed Women and Men With and Without Concurrent Panic Attacks

men. There were significant differences in mean ΔTSH30 between depressed men with panic and normal subjects and between depressed men with and without panic.

Previous reports of TRH testing in panic disorder

patients (18–20) have treated ΔTSH as a dichotomous variable, with $\Delta\text{TSH30} < 7.0 \mu\text{U/ml}$ defined as a low response of TSH to TRH, paralleling numerous studies of TSH response to TRH in depression (12). While recognizing that ΔTSH30 is actually a continuous variable, for conventional descriptive purposes, we dichotomized our data by using ΔTSH30 of $7.0 \mu\text{U/ml}$ as the arbitrary threshold. According to this criterion, four of 10 depressed women with panic (40%) had low TSH response, whereas only three of 17 depressed women without panic (18%) and seven of 38 normal women (18%) had a low response. For men, three of four depressed subjects with panic (75%) had a low TSH response, whereas only four of 15 depressed subjects without panic (27%) and 16 of 68 normal subjects (23%) had a low response.

We analyzed body surface area, baseline serum cortisol, TSH and free thyroxine index, duration and severity of present illness, and interval since first depressive episode as possible confounding variables for the association between current panic attacks and low ΔTSH30 among depressed patients. For each gender, the relationship between current panic attacks and low ΔTSH30 remained statistically significant ($p < 0.05$) after adjustment for each of the variables listed earlier. The reciprocal analysis to detect the effect of each covariable on ΔTSH30 beyond that explained by panic showed that only baseline serum cortisol was significant ($p < 0.05$) for both genders. Interval since first depressive episode was significant ($p < 0.05$) for women only, and baseline free thyroxine index and TSH for men only ($p < 0.05$). Women with long-standing panic attacks persisting into their current depressive episode had a significantly greater prevalence of low ΔTSH30 than women with panic attacks only during their depressive episode (one-tailed Fisher's exact test, $p < 0.04$).

We also analyzed for differences in ΔTSH30 between depressed subjects with and without RDC endogenous subtype. This method of subtyping depressed subjects revealed no statistically significant differences (for women, $t = 1.55$, $df = 25$, $p = 0.13$; for men, $t = 0.38$, $df = 17$, $p = 0.71$). However, subdividing endogenously depressed patients into those with and without concurrent panic attacks revealed significantly lower mean \pm SD ΔTSH30 in seven women with panic than in 11 women without panic (9.8 ± 4.5 versus $16.1 \pm 7.5 \mu\text{U/ml}$; $t = -1.97$, $df = 16$, $p = 0.03$) and a trend toward lower mean ΔTSH30 in two men with panic than in nine men without panic (4.4 ± 1.0 versus $9.1 \pm 4.1 \mu\text{U/ml}$; $t = 1.54$, $df = 9$, $p = 0.08$).

The t tests showed no statistically significant correlation, for either gender, between hypnotic or anxiolytic medication and low TSH response to TRH (for women, $t = 0.93$, $df = 25$, $p = 0.37$; for men, $t = 1.17$, $df = 17$, $p = 0.26$). Furthermore, we have shown in pilot work with normal male volunteers that up to 50 mg of oral chlordiazepoxide has no effect on TSH response to intravenous TRH (21).

DISCUSSION

The results of this investigation confirm our hypotheses that depressed patients with concurrent panic attacks have a higher prevalence of low TSH response to TRH and a lower mean TSH response than either depressed patients without current panic attacks or normal subjects. The hypothesis is confirmed for each gender separately and when the influence of possibly confounding variables is considered. The argument is further strengthened by the finding that even within the endogenous subtype of depressed patients, the presence of panic attacks still correlated significantly with low Δ TSH30. Finally, although duration of current depressive episode failed to correlate with low Δ TSH30, the women in our study did show a significant association between recurring, long-standing panic attacks that antedated onset of their current depressive episode and low Δ TSH30. These observations strongly suggest that panic may be an important indicator or determinant of hypothalamic-pituitary-thyroid axis pathology in depressed patients. The findings are particularly interesting in light of the absence of similarly powerful psychopathologic predictors of low TSH response in the depressed population.

Despite methodologic differences from the present investigation, prior studies of TRH testing in nondepressed patients with panic disorder have consistently reported a low TSH response (18–20). The results in these studies are similar to those of the current report, whether Δ TSH is treated as a continuous or dichotomous variable. The mean Δ TSH30 values of our male and female depressed patients with concurrent panic attacks (table 1) are comparable to the mean Δ TSH of 8.4 μ U/ml reported by Roy-Byrne et al. (19) and mean Δ TSH of 8.3 IU/ml reported by Hamlin and Pottash (20) in mixed gender samples. It is unclear whether any patients studied by Hamlin and Pottash (20) and by Schweizer et al. (18) had prior histories of depression. However, Roy-Byrne et al. indicated that some of their panic disorder subjects had prior histories of major depression, although they did not meet the RDC for major, minor, or intermittent depression when TRH tested. Nevertheless, their panic patients with and without prior depression had similar TSH responses to TRH.

Figure 1 illustrates two points that deserve particular emphasis. In addition to confirming the hypothesis that depressed patients with panic have lower mean Δ TSH30 than normal subjects and than depressed patients without panic, the data show that depressed patients without panic are indistinguishable from normal subjects by TRH testing. However, the lower mean Δ TSH30 of depressed patients with panic is not primarily the result of greater prevalence of responses at the low end of the Δ TSH30 range. In fact, perhaps the most striking feature of the scatterplots is the complete absence of responses at the high end of the Δ TSH30 range for both male and female depressed patients with concurrent panic attacks. This novel descriptive

feature of TSH response to TRH in psychiatric patients deserves replication and explanation.

Two hypotheses have been proposed to account for low TSH response to TRH in apparently euthyroid psychiatric patients (12, 13). The first proposes chronic TRH hypersecretion with consequent hyporesponsiveness of anterior pituitary thyrotroph cells, possibly due to down-regulation of TRH receptors. High noradrenergic input and low serotonergic input to hypothalamic TRH-secreting cells are suggested as possible mechanisms for chronic hypersecretion of TRH, although human evidence supporting these explanations remains tenuous. The second hypothesis suggests that thyrotroph cells either are primarily disordered or are inhibited from releasing TSH by known (thyroid hormones, cortisol, or dopamine) or unknown inhibitory substances. Although thyroid hormones are the most potent inhibitors of TSH secretion, they have often been dismissed as an explanation for TSH hyposecretion in psychiatric populations because subjects in most of these studies had normal baseline thyroid hormone levels. These hypotheses may be considered in three contexts: the proposed neurobiologic substrate of panic attacks, recent discoveries about the biology of low TSH response in nonpsychiatric subjects, and the relationship of panic to thyroid hormone state.

Redmond (22) has recently reviewed a wide range of evidence suggesting that higher noradrenergic activity of locus ceruleus neurons underlies panic attacks. Locus ceruleus neurons have projections to the hypothalamus and therefore could be the source of higher noradrenergic input, which is postulated as a mechanism of chronic TRH hypersecretion (12, 13).

Snyder and Utiger (23) have demonstrated that treating normal subjects for several weeks with quantities of T_3 and T_4 sufficient to raise their serum T_3 , while still maintaining it within normal limits, results in a 76% decrease in maximal TSH response to 400 μ g of TRH; this finding indicates exquisite sensitivity of TSH release to changes in circulating T_3 within physiological range. Recent reports in the endocrinologic literature have begun to clarify the pathophysiology of chemically euthyroid nonpsychiatric patients with low TSH response to TRH. Such patients have been described as having thyroid hypersensitivity to TSH (24), higher free T_3 and free T_4 that often evolves into overt hyperthyroidism (25), and high T_3 production rate and low basal TSH, with an inverse correlation between basal TSH and both total and free T_3 (26).

Resonating with these studies are reports that thyroid hormone levels do in fact contribute to the low TSH response to TRH in depressed patients. Calloway et al. (14) found that depressed patients with low TSH response had higher free thyroxine index values than depressed patients with normal response. Kirkegaard and Faber (27) reported an association between low TSH response and directly measured free T_4 levels. However, many studies of psychiatric patients have not demonstrated a clear relationship between thyroid hormone levels and TSH response (12).

In summary, these endocrinologic and psychiatric reports raise anew the question of "preclinical" or "marginal" hyperthyroidism as a mechanism of low TSH response in psychiatric patients. Overt hyperthyroidism has been associated with anxiety, irritability, and motor tension (28), a wide variety of simple phobias (29), and agoraphobia, usually with panic attacks (30). A recent study of panic disorder patients found four of 55 with high T_3 , T_4 , or free thyroxine index (31). Another study of thyroid indices in panic disorder patients found that none of 82 patients had abnormal total T_4 or T_3 resin uptake, but 11 of 51 patients had undetectable ($<0.5 \mu\text{U/ml}$) basal TSH (32).

Although we did not find lower basal TSH levels in our depressed subjects with concurrent panic attacks, the TSH radioimmunoassay we employed for this study lacked the sensitivity for very low levels of TSH that is available in newer immunoradiometric assays. We intend to employ more sensitive provocative and kinetic measurements such as those cited from the endocrinologic literature to elucidate the presence and mechanism of "marginal" hyperthyroidism in psychiatric patients. The present study suggests that depressed patients with panic differ biologically from depressed patients without panic. Furthermore, depressed patients with panic apparently represent a target population likely to yield more refined information about dysregulation of the hypothalamic-pituitary-thyroid axis in psychiatric disorders.

REFERENCES

- Breier A, Charney DS, Heninger GR: Major depression in patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 1984; 41:1129-1135
- Uhde TW, Boulenger JP, Roy-Byrne PP, et al: Longitudinal course of panic disorder: clinical and biological considerations. *Prog Neuropsychopharmacol Biol Psychiatry* 1985; 9:39-51
- VanValkenberg C, Winokur G, Behar D, et al: Depressed women with panic attacks. *J Clin Psychiatry* 1984; 45:367-369
- Robinson DS, Kayser A, Corcella J, et al: Panic attacks in outpatients with depression: response to antidepressant treatment. *Psychopharmacol Bull* 1985; 21:562-567
- Leckman JF, Weissman MM, Merikangas KR, et al: Panic disorder and major depression: increased risk of depression, alcoholism, panic and phobic disorders in families of depressed probands with panic disorder. *Arch Gen Psychiatry* 1983; 40:1055-1060
- Weissman MM, Leckman JF, Merikangas KR, et al: Depression and anxiety disorders in parents and children: results from the Yale Family Study. *Arch Gen Psychiatry* 1984; 41:845-852
- Sheehan DV, Ballenger J, Jacobsen G: Treatment of endogenous anxiety with phobic, hysterical and hypochondriacal symptoms. *Arch Gen Psychiatry* 1980; 37:51-59
- Lake CR, Pickar D, Ziegler MG, et al: High plasma norepinephrine levels in patients with major affective disorder. *Am J Psychiatry* 1982; 139:1315-1318
- Nesse RM, Cameron OG, Curtis GC, et al: Adrenergic function in patients with panic anxiety. *Arch Gen Psychiatry* 1984; 41:771-776
- Brown R, Kocsis JH, Caroff S, et al: Differences in nocturnal melatonin secretion between melancholic depressed patients and control subjects. *Am J Psychiatry* 1985; 142:811-816
- McIntyre IM, Norman TR, Marriott PF, et al: The pineal hormone melatonin in panic disorder. *J Affective Disord* 1986; 12:203-206
- Loosen PT, Prange AJ: Serum thyrotropin response to thyrotropin-releasing hormone in psychiatric patients: a review. *Am J Psychiatry* 1982; 139:405-416
- Loosen PT: The TRH-induced TSH response in psychiatric patients: a possible neuroendocrine marker. *Psychoneuroendocrinology* 1985; 10:237-260
- Calloway SP, Dolan RJ, Fonagy P, et al: Endocrine changes and clinical profiles in depression, II: the thyrotropin-releasing hormone test. *Psychol Med* 1984; 14:759-765
- Kirstein L, Gold MS, Extein I, et al: Clinical correlates of the TRH infusion test in primary depression. *J Clin Psychiatry* 1982; 43:191-194
- Linkowski P, Van Wettere JP, Kerkhofs M, et al: Thyrotropin response to thyrostimulin in affectively ill women: relationship to suicidal behavior. *Br J Psychiatry* 1983; 143:401-405
- Takahashi S, Kondo H, Yoshimura M, et al: Thyrotropin responses to TRH in depressive illness: relation to clinical subtypes and prolonged duration of depressive episode. *Folia Psychiatr Neurol Jpn* 1974; 28:355-365
- Schweizer E, Winokur A, Rickels K: Neuroendocrine function in panic disorder. Abstracts of the Fortieth Annual Convention and Scientific Program of the Society of Biological Psychiatry. Dallas, SBP, 1985
- Roy-Byrne PP, Uhde TW, Rubinow DR, et al: Reduced TSH and prolactin responses to TRH in patients with panic disorder. *Am J Psychiatry* 1986; 143:503-507
- Hamlin CL, Pottash ALC: Evaluation of anxiety disorders, in *Diagnostic and Laboratory Testing in Psychiatry*. Edited by Gold MS, Pottash ALC. New York, Plenum, 1986
- Garbutt JC, Gillette GM, Mason GA, et al: TRH-chlordiazepoxide (CDZ) interactions in man. Abstracts of the Forty-Second Annual Convention and Scientific Program of the Society of Biological Psychiatry. Chicago, SBP, 1987
- Redmond DE: Studies of the nucleus locus coeruleus in monkeys and hypotheses for neuropsychopharmacology, in *Psychopharmacology: The Third Generation of Progress*. Edited by Meltzer HS. New York, Raven Press, 1987
- Snyder PJ, Utiger RD: Inhibition of thyrotropin response to thyrotropin-releasing hormone by small quantities of thyroid hormones. *J Clin Invest* 1972; 51:2077-2084
- Boutin JM, Matte R, D'Amour P, et al: Characteristics of patients with normal T_3 and T_4 and a low TSH response to TRH. *Clin Endocrinol* 1986; 25:579-588
- Lerro S, Losa M, Trisorio MT, et al: Free thyroid hormone levels and TSH response to TRH in patients with autonomous thyroid adenomata and normal T_3 and T_4 . *Clin Endocrinol* 1985; 23:373-378
- Bregengard C, Kirkegaard C, Faber J, et al: Relationships between serum thyrotropin, serum free thyroxine (T_4), and 3,5,3',5'-triiodothyronine (T_3) and the daily T_4 and T_3 production rates in euthyroid patients with multinodular goiter. *J Clin Endocrinol Metab* 1987; 65:258-261
- Kirkegaard C, Faber J: Influence of free thyroid hormone levels on the TSH response to TRH in endogenous depression. *Psychoneuroendocrinology* 1986; 11:491-497
- Whybrow PC, Prange AJ, Treadway CR: Mental changes accompanying thyroid gland dysfunction. *Arch Gen Psychiatry* 1969; 20:48-63
- Ficarra BJ, Nelson RA: Phobia as a symptom in hyperthyroidism. *Am J Psychiatry* 1947; 103:831-832
- Lindemann CG, Zitrin CM, Klein DF: Thyroid dysfunction in phobic patients. *Psychosomatics* 1984; 25:603-606
- Matuzas W, Al-Sadir J, Uhlenhuth EH, et al: Mitral valve prolapse and thyroid abnormalities in patients with panic attacks. *Am J Psychiatry* 1987; 144:493-496
- Fishman SM, Sheehan DV, Carr DB: Thyroid indices in panic disorder. *J Clin Psychiatry* 1985; 46:432-433

Hypnotic Alteration of Somatosensory Perception

David Spiegel, M.D., Pierre Bierre, M.S., and John Rootenberg, B.A.

Effects of hypnotic alterations of perception on amplitude of somatosensory event-related potentials were studied in 10 highly hypnotizable subjects and 10 subjects with low hypnotizability. The highly hypnotizable individuals showed significant decreases in amplitude of the P₁₀₀ and P₃₀₀ waveform components during a hypnotic hallucination that blocked perception of the stimulus. When hypnosis was used to intensify attention to the stimulus, there was an increase in P₁₀₀ amplitude. These findings are consistent with observations that highly hypnotizable individuals can reduce or eliminate pain by using purely cognitive methods such as hypnosis. Together with data from the visual system, these results suggest a neurophysiological basis for hypnotic sensory alteration.

(Am J Psychiatry 1989; 146:749-754)

Highly hypnotizable individuals are capable of profound alterations in subjective experience, including the ability to reduce or eliminate pain, control anxiety, and produce hallucinations. Despite these intense and unusual subjective experiences, there has been little objective evidence of any accompanying neurophysiological change. If such phenomena involve more than mere subjective report, they should be reflected in altered processing of perception as measured by scalp electrodes. Cortical event-related potentials provide a useful test for studying perceptual and attentional processes in humans (1, 2). Event-related potentials are scalp EEG recordings time-locked to a series of approximately 50-100 perceptual stimuli, making it

possible to study brain electrical activity associated with perception of and neural response to the stimulus series. The amplitudes of the early components (100-200 msec after the stimulus) of event-related potentials reflect exogenous factors: the intensity of the stimulus and the process of selecting the perceptual channel that is used, such as visual versus auditory (3-5). That is, the stronger the input signal, the larger the amplitude of electrical activity approximately 100 msec after the stimulus has been presented, especially over the respective sensory-association cortex. The amplitudes of the later components (200-500 msec after the stimulus) are influenced by endogenous factors such as response to perception of the stimuli, by the degree to which the stimuli are unexpected (2, 5-9), and by the extent to which the stimuli are consciously perceived (10, 11). For example, stimuli that are rare, that require a response, or that demand conscious attention tend to produce larger positive amplitudes approximately 300 msec after the stimuli have been presented, especially at frontal (reflecting infrequency) and parietal (reflecting task relevance) recording sites (2, 12). In the present study, we examined the effects on event-related potential amplitudes of somatosensory perceptual distortion produced by hypnosis. This sensory alteration is analogous to that which is used successfully in clinical pain control techniques involving hypnosis.

Previous findings in this area have been inconsistent. Some studies (13-17) have shown reduction in the amplitude of visual or auditory event-related potentials when hypnotized subjects were instructed to attenuate perception of a stimulus or focus attention on a competing stimulus. Other studies (18-24) have failed to confirm such a relationship between hypnotic attention and amplitude of event-related potentials. There are several reasons for this disparity. The nature of the hypnotic instruction is critical to the outcome. A suggestion that a subject attenuate or diminish the apparent brightness of a stimulus requires that the subject pay attention to it. Thus, the process of following such a hypnotic instruction contradicts its content. Similarly, instructing subjects that they will not perceive anything at all may result in a startle response that increases rather than decreases the amplitude of event-related potentials if the obstruction is less than perfect (25-27). Other limitations of some studies include small sample sizes, the use of patients with severe neurological or psychiatric disorders, and semiquantitative analysis of event-related potentials. In one study

Presented at the 141st annual meeting of the American Psychiatric Association, Montreal, May 7-12, 1988. Received July 12, 1988; revision received Nov. 8, 1988; accepted Dec. 2, 1988. From the Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine. Address reprint requests to Dr. Spiegel, Department of Psychiatry and Behavioral Sciences, Stanford University Medical Center, Stanford, CA 94305.

Supported by the John D. and Catherine T. MacArthur Foundation and the Alan and Laraine Fischer Foundation.

The authors thank Dr. Karl Pribram for consultation and review, Mark Mitchell for statistical programming, Anne Noel and Kanji Takahashi for research assistance, Dr. Cecil Bridges for recording system engineering, Dr. Helena Kraemer for statistical consultation, and Drs. Helen Blau, Jess Ghannam, Ernest R. Hilgard, Walton T. Roth, Charles Shagass, and Charles Yingling for review and critique of the manuscript.

Copyright © 1989 American Psychiatric Association.

(27), highly hypnotizable subjects were instructed to replace the stimulus with a competing image rather than reduce or eliminate it. This resulted in a general reduction of event-related potential amplitude that was statistically significant for the P_{300} portion of the waveform throughout the scalp. In the present study we sought to demonstrate that altered event-related potentials are not specific to the visual system, but are also observed in the somatosensory system and may be a measure of altered perception induced by hypnosis.

We studied the effects of hypnotic perceptual alteration in the somatosensory system. This sensory modality was chosen because hypnosis has been shown to be an effective tool in pain reduction (28–30). Although we studied electrical stimulation that was beneath the pain threshold, the analogy to hypnotic analgesia holds: the event-related potential waveform does not differ in response to noxious versus subnoxious somatosensory stimulation (31). Our hypothesis was that when highly hypnotizable individuals experienced reduction or elimination of their perception of a somatic stimulus, they would produce event-related potentials with lower amplitudes. We predicted that this effect would be especially strong at P_{300} , since this component of the waveform is influenced by the relevance of the stimulus and was the point of reduction most prominently observed in our study of the effects of obstructive hallucination in the visual system (27). Conversely, we sought to assess whether hypnotized subjects who were instructed to enhance attention to the somatosensory stimulus would demonstrate correspondingly increased amplitudes of event-related potentials. It was expected that these effects would be greatest in the parietal (somatosensory association) region contralateral to the stimulus.

METHOD

Two groups of subjects, 10 high and 10 low in hypnotizability, were selected on the basis of consistently high (8 to 12) or low (0 to 4) scores on the Harvard Group Scale of Hypnotic Susceptibility, Form A (32) and the Stanford Hypnotic Susceptibility Scale, Form C (33). These differences were confirmed with the Hypnotic Induction Profile (34). Informed consent was obtained after the nature and possible consequences of the study had been fully explained in accordance with the Stanford Human Subjects Committee guidelines. A total of 20 right-handed subjects, seven men and three women in each group, performed the experiment.

Four randomly ordered instruction conditions were used, during which subjects were given identical somatosensory stimulation while event-related potentials were recorded. In each instruction condition, subjects received 110 electrical stimuli. There were 99 single (standard) stimuli from which event-related potential recordings were drawn, mixed randomly with 11 triple (target) stimuli to which the subjects were expected to press a button (35). This was done to ensure maximal

attention to the stimuli, allowing us to monitor the subjects' accuracy in identifying targets (36). The interstimulus interval was rectangularly distributed between 4.0 and 5.0 seconds. The EEG was digitally recorded from seven monopolar leads (F_3 , F_4 , Cz , P_3 , P_4 , O_1 , and O_2) referenced to a lead linking the mastoid processes behind the left and right ears; the electro-oculogram (EOG) was recorded as a bipolar channel to measure eye movement artifact.

The somatosensory stimuli consisted of biphasic pulses of 1.6-msec duration applied over the left radial nerve at the palmar surface of the wrist. Pulses were generated by means of a Grass SD-9 stimulator triggered externally by the recording PDP-11 computer. Stimulus electrodes were placed longitudinally along the radial nerve approximately 2 cm apart; the proximal lead had negative polarity. A subjective "base level" of pulse intensity (voltage) was established by using descending levels of stimulation until a level was reached that the subject perceived as just below the threshold of discomfort. This resulted in stimuli between 1.2 and 2.0 times the subject's threshold of sensation. To compensate for habituation to the stimulus, the voltage was adjusted slightly upward after each experimental condition to reestablish the subjective base level. Stimulus interelectrode skin resistance varied from subject to subject between 29 and 325 k Ω but did not change during the procedure with the use of biphasic stimuli. Mean \pm SD skin resistance for the highly hypnotizable subjects was 106 ± 108 k Ω ; for the subjects with low hypnotizability it was 208 ± 164 k Ω .

While this difference was not statistically significant, it did raise the possibility of between-group differences in stimulus intensity. This, however, was not the case. During the protocol the highly hypnotizable subjects had a slightly lower mean \pm SD threshold voltage (14.1 ± 10.1 versus 16.8 ± 7.7 V), but at a higher mean \pm SD threshold current (168 ± 82 versus 103 ± 48 μ A), as would be expected by virtue of lower skin resistance. Likewise, their average-run voltage was lower (19.2 ± 14.7 versus 27.1 ± 10.6 V), but their average-run current was higher (256 ± 123 versus 172 ± 70 μ A). The ratio of stimulus to threshold current averaged 1.5 ± 0.3 for the highly hypnotizable subjects and 1.7 ± 0.5 for the subjects with low hypnotizability. None of these differences was statistically significant.

An EEG recording helmet with Beckman silver-silver chloride recording electrodes mounted on 25-mm extender tubes with saline-soaked tips was used for the seven scalp and two mastoid sites. The EOG was recorded from two Grass gold-cup electrodes located on the lower orbital ridge and on the outer canthus of the right eye. The EEG was amplified 50,000 times and the EOG 5,000 times by means of Grass P511K amplifiers with flat gain (to within -3 dB) between 1 Hz and 100 Hz, except for a notch filter at 60 Hz. Incoming signals were amplified and digitally sampled at 4-msec intervals with 0.1- μ V amplitude resolution. Each recording epoch consisted of a 200-msec prestimulus baseline and an 800-msec poststimulus onset record. Epochs

were sorted by stimulus type (standard stimuli versus target stimuli that required button pressing), and the target stimuli were eliminated, leaving 99 standard-stimulus epochs for further processing of event-related potentials. Epochs were then rejected for the following reasons: 1) false positives (button pressing on standard [nontarget] stimuli), 2) muscle artifact contamination, 3) outliers resulting from analog to digital conversion clipping, and 4) alpha-rhythm bursts. This process yielded a mean \pm SD of 67 ± 26 nontarget epochs per condition for the highly hypnotizable subjects and 70 ± 25 per condition for the subjects with low hypnotizability. Epochs were arithmetically averaged (preserving amplitude for stimulus-locked waveform components), normalized to a 0- μ V baseline average level, smoothed using a two-pass, three-point Hanning function, and graphed.

The six standard event-related potential components (P_{100} , N_{150} , P_{200} , N_{250} , P_{300} , and N_{400}) were maximal or minimal amplitudes occurring in intervals defined by the following process. 1) All event-related potential curves from all subjects, all experimental conditions, and all recording sites were arithmetically combined into one grand total curve. 2) The maximal and minimal amplitudes were identified. 3) The half-amplitude level between neighboring peaks (e.g., halfway in amplitude between N_{150} and P_{200}) was established. 4) The point in time on the abscissa of this half-amplitude became the dividing boundary (e.g., between the N_{150} and the P_{200} windows). 5) Within each latency window, a maxima/minima finder was used to locate the amplitude and latency for each of the six event-related potential components for each subject in each condition. To test the experimental hypothesis, one three-way analysis of variance (ANOVA) (Group by Condition by Recording Site) was conducted for amplitude of event-related potentials at each of the six component peaks. The randomized presentation of attention conditions reduced the likelihood that unequal serial correlations would affect this analysis. Post hoc testing was conducted only when preceded by a significant overall ANOVA.

Four experimental attention conditions were presented in random order. In the normal attention condition, the subjects were instructed to press a button each time they felt the target stimulus. In the passive attention condition, the subjects were instructed to attend to the stimuli but not press the button. In the hypnotic attention condition, the subjects were first led through a hypnotic-induction exercise that involved closing the eyes and elevating the left hand in response to an instruction that it would feel "light and buoyant." These movements provided behavioral confirmation that the subjects were complying with instructions. They were then instructed to attend carefully to the stimuli, which they were told to experience as "pleasant and interesting," and press the button in response to targets. In the hypnotic obstructive hallucination condition, the hypnotic-induction exercise was followed by the hypnotic suggestion that a local anes-

thetic, such as Novocain, was spreading from fingers to hand to forearm of the stimulated limb. Subjects were further instructed to make the limb cold, tingling, and numb. They were then told to press the button if they felt any of the target stimuli. The experimenter conducting the hypnosis session was blind to the subjects' hypnotizability scores to ensure that all subjects received identical instructions. This was important, since highly hypnotizable individuals are especially sensitive to interpersonal cues (37, 38).

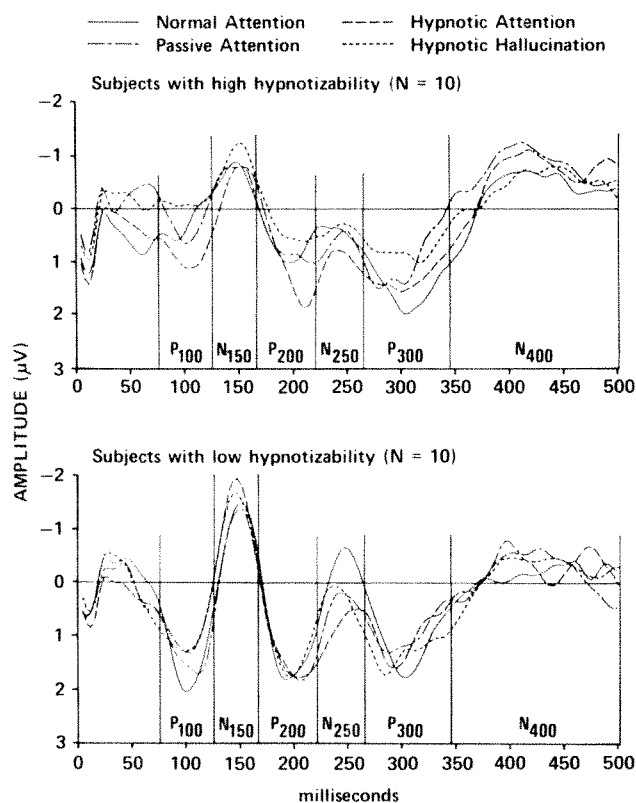
RESULTS

The highly hypnotizable subjects were able to suppress perception of the stimulus in the hallucination condition as measured by behavioral criteria. There was a significant Group by Condition difference in button pressing ($F=10.04$, $df=2, 36$, $p<0.001$) after elimination of the passive attention condition, which required no button pressing. The highly hypnotizable subjects pressed the button in response to 38% of the targets in the hypnotic obstructive hallucination condition, while the subjects with low hypnotizability pressed the button in response to 80% of the targets in that condition. In contrast, no significant differences were seen during the control conditions: both groups of subjects pressed the button in response to 86% or more of the targets in the normal attention and hypnotic attention conditions.

Among the highly hypnotizable subjects this perceptual suppression was accompanied by a reduction in amplitude of event-related potentials. There was a significant Group by Condition effect in the predicted direction on the amplitude of the event-related response. Figure 1 indicates, first, that the mean amplitudes of event-related potentials were lower for the subjects with high hypnotizability than for those with low hypnotizability regardless of condition. Indeed, the mean \pm SD P_{100} amplitude was significantly lower among the highly hypnotizable subjects than among those with low hypnotizability (1.41 ± 0.93 versus 2.55 ± 1.82 μ V; $F=4.56$, $df=1, 18$, $p<0.04$). These differences were not expected, but they are consistent with a trait rather than a state conception of hypnotizability. If this interpretation is accepted, the data of interest in the present experiment are the changes from the baseline normal attention condition produced by the different experimental conditions. Therefore, a second ANOVA was performed on the difference between the normal attention condition and the other conditions at P_{100} to test the hypothesis that the highly hypnotizable subjects would show differences in amplitude among conditions which would not be seen in the subjects with low hypnotizability.

At the P_{100} portion of the waveform there was a significant Group by Condition interaction throughout the scalp ($F=3.61$, $df=2, 36$, $p<0.02$). Of the eight mean P_{100} amplitudes (2 groups \times 4 conditions), the highly hypnotizable subjects had the lowest mean \pm SD

FIGURE 1. Mean Amplitudes of Somatosensory Event-Related Potentials in Four Conditions for Subjects With High and Low Hypnotizability



amplitudes in the hypnotic obstructive hallucination condition ($0.80 \pm 0.71 \mu\text{V}$ versus $1.45 \pm 0.90 \mu\text{V}$ in the normal attention condition and $1.45 \pm 0.76 \mu\text{V}$ in the passive attention condition) (see figure 1). It appears, from subsequent matched-pairs *t* test comparisons (permitted by this ANOVA) among the highly hypnotizable subjects, that P_{100} amplitude during the hypnotic obstructive hallucination condition was lower than it was during the passive attention condition and the hypnotic attention condition. Indeed, these subjects exhibited the lowest mean P_{100} amplitudes in the hypnotic obstructive hallucination condition at all seven recording sites. During this condition, P_{100} amplitude was reduced by 45% relative to normal attention. By contrast, the subjects with low hypnotizability did not show a significant difference in amplitude among conditions.

In addition to lower P_{100} amplitudes, the highly hypnotizable subjects demonstrated lower P_{300} amplitudes during the hypnotic obstructive hallucination condition. There was a significant Group by Condition by Recording Site interaction for P_{300} amplitude ($F=1.9$, $df=18, 324$, $p<0.05$) (see figure 1). Highly hypnotizable subjects' P_{300} amplitudes were lower during hypnotic hallucination than during both normal attention and passive attention at the right frontal, parietal, and occipital leads (F_4 , P_4 , and O_2) and were lower than those during normal attention only at O_1 as well. The

only similar difference observed among the subjects with low hypnotizability was at O_2 , but, contrary to task instruction, hypnotic attention amplitudes were reduced as well at O_2 .

In contrast, in the highly hypnotizable subjects, an increase of 35% in mean P_{100} amplitude was observed during hypnotic attention ($1.95 \pm 0.91 \mu\text{V}$) as compared with that during normal attention ($1.45 \pm 0.90 \mu\text{V}$). Indeed, the increase in P_{100} amplitude during hypnotic attention was greater than the change observed during both the passive attention and hypnotic hallucination conditions.

Thus, the highly hypnotizable subjects showed bidirectional task-related changes: increased P_{100} amplitude during hypnotic attention and decreased P_{100} and P_{300} amplitudes during hypnotic hallucination, whereas the subjects with low hypnotizability did not. An examination of standardized interaction terms for the amplitude changes among conditions indicated that the primary effect at P_{100} was the relative increase in amplitude during the hypnotic attention condition among the highly hypnotizable subjects ($+0.48 \mu\text{V}$), while the predominant effect at P_{300} was the relative decrease in amplitude during the hypnotic hallucination condition ($-0.33 \mu\text{V}$).

DISCUSSION

The results of this study confirmed the hypothesis that highly hypnotizable subjects would show task-related changes in the amplitudes of their somatosensory event-related responses. The amplitude of the highly hypnotizable subjects' P_{100} event-related potentials was increased during hypnotic attention and substantially reduced during hypnotic obstruction, as was the amplitude of their P_{300} potentials. Such task-related differences were not observed among the subjects with low hypnotizability. Thus, hypnosis-induced subjective changes in perception were accompanied by congruent alterations in amplitude of event-related potentials. These results confirm our previous findings in the visual system (27). However, the reduction in event-related response to the somatosensory stimuli occurred not only at P_{300} , as previously observed in the visual system, but also earlier, at P_{100} .

How can these changes in amplitude of event-related potentials be explained? This new finding may relate to the prominence of P_{100} components in somatosensory event-related potentials (36, 39, 40). Nonhypnotic suppression of somatosensory event-related potentials has been observed when there is cognitive dissonance regarding a painful stimulus that motivates the subject to suppress it (41) and during effects of analgesic drugs (42). An analogy may be drawn between signal detection theory and the early and late components of the event-related potential: the early components reflect more the effect of signal detection; the later components, response bias or interpretation of the signal. While P_{300} amplitude increases with better signal de-

tection (2, 43), it is strongly increased by stricter response bias (44)—for example, confidence in the evaluation of a detected signal as painful.

Which is involved in hypnotic analgesia? Schizophrenic patients were shown to have lower P_{100} , N_{120} , and P_{200} amplitudes than normal subjects in response to marginally painful stimuli (45). The between-group differences in signal detection disappeared with administration of naloxone, an opiate antagonist, while response bias differences did not. However, since hypnotic analgesia is not reversed by the administration of naloxone (46, 47), the present findings seem to suggest that hypnotic alteration of pain perception operates at the level of the response bias by reducing the painfulness of the stimulus rather than the detection of the signal (48). The fact that we found effects at P_{100} as well as at P_{300} suggests that alteration in signal detection may also be involved.

P_{300} amplitude is influenced by several factors: stimulus infrequency, task relevance, attention (2, 5–9), novelty (12), and conscious processing (10, 11). In the present experiment, the expectancy (frequency) of stimuli was held constant across conditions, but the other variables could have been influenced by hypnotic hallucination. Hypnosis has long attracted interest because of its role in altering the boundary between conscious and unconscious experience (28, 34). The hypnotic hallucination may have made perception of the stimulus less conscious, relevant, or novel.

The strong involvement of the frontal region may be of particular importance, since it suggests that the signal generator for the hallucinated image which reduced attention to the sensory stimulus may be located frontally or in subcortical structures which project to the frontal cortex. It may also mean that the strength of the normally perceived signal is due in part to processing by the right frontal cortex, which has been shown to be involved in recognition of novel stimuli (49, 50). Reduction in right frontal processing may make the stimulus seem routine and thereby reduce its signal strength.

The difference in overall P_{100} amplitude between highly hypnotizable subjects and subjects with low hypnotizability was unexpected. We found no such differences in hypnotizability in our study of visual event-related response, but it is conceivable that these are trait differences that reflect different styles of somatosensory information processing, with highly hypnotizable subjects being more capable of turning to inward imagined experience (51) and thereby suppressing somatosensory perception.

Highly hypnotizable subjects, but not those with low hypnotizability, showed changes in amplitude of event-related potentials consistent with hypnotic task demands. This study suggests that such sensory alterations are accomplished by an alteration in neuronal response to stimuli. These findings provide evidence that hypnotically induced subjective changes such as anesthesia or visual hallucinations involve alterations in perceptual processing. Further, they demonstrate a

neurophysiological difference between individuals with high and low hypnotizability. Such findings provide a basis for further exploring the neurophysiological mechanism underlying hypnotic analgesia.

REFERENCES

1. Donchin E, Ritter W, McCallum WC: Cognitive psychophysiology: the endogenous components of the ERP, in *Event-Related Brain Potentials in Man*. Edited by Callaway E, Tueting P, Koslow SH. New York, Academic Press, 1978
2. Pritchard WS: Psychophysiology of P_{300} . *Psychol Bull* 1981; 89: 506–540
3. Ford JM, Roth WT, Dirk SJ, et al: Evoked potential correlates of signal recognition between and within modalities. *Science* 1978; 181:465–466
4. Hillyard SA, Picton TW: Event-related brain potentials and selective information processing in man, in *Progress in Clinical Neurophysiology*, vol 6. Edited by Desmedt JE, Basel, S Karger, 1979
5. Sutton S, Braren M, Zubin J: Evoked-potential correlates of stimulus uncertainty. *Science* 1965; 150:1187–1188
6. Hillyard SA, Picton TW: Sensation, perception, and attention: analysis using ERPs, in *Event-Related Brain Potentials in Man*. Edited by Callaway E, Tueting P, Koslow SH. New York, Academic Press, 1978
7. Duncan-Johnson CC, Donchin E: The relation of P_{300} latency to reaction time as a function of expectancy. *Prog Brain Res* 1980; 54:717–722
8. Johnson R: P_{300} amplitude and probabilistic judgments. *Prog Brain Res* 1980; 54:723–729
9. Baribeau-Braun J, Picton TW, Gosselin JU: A neurophysiological evaluation of abnormal information processing. *Science* 1983; 219:874–876
10. Posner MI, Klein R, Summers J, et al: On the selection of signals. *Memory and Cognition* 1973; 1:2–12
11. Posner MI: *Chronometric Explorations of Mind*. Hillsdale, NJ, Lawrence Erlbaum Associates, 1978
12. Squires KC, Squires NK, Hillyard SA: Decision-related cortical potentials during an auditory signal detection task with cued observation intervals. *J Exp Psychol [Hum Percept]* 1975; 1: 268–279
13. Clynes M, Kohn M, Lifshitz K: Dynamics and spatial behavior of light-evoked potentials, their modification under hypnosis, and on-line correlation in relation to rhythmic components. *Ann NY Acad Sci* 1964; 112:468–509
14. Galbraith GC, Cooper LM, London P: Hypnotic susceptibility and the sensory evoked response. *J Comp Physiol Psychol* 1972; 80:509–514
15. Guerrero-Figueroa R, Heath RG: Evoked responses and changes during attentive factors in man. *Arch Neurol* 1964; 10: 74–84
16. Hernandez-Peon R, Donoso M: Influence of attention and suggestion upon subcortical evoked electric activity in the human brain, in *First International Congress of Neurological Sciences*, vol 3. Edited by Van Bogaert L, Radermecker J. London, Pergamon Press, 1959
17. Wilson NJ: Neurophysiologic alterations with hypnosis. *Dis Nerv Syst* 1968; 19:618–620
18. Amadeo M, Yanovski A: Evoked potentials and selective attention in subjects capable of hypnotic analgesia. *Int J Clin Exp Hypn* 1975; 23:200–210
19. Andreassi JL, Balinsky B, Gallichio JA, et al: Hypnotic suggestion of stimulus change and visual cortical evoked potential. *Percept Mot Skills* 1976; 42:371–378
20. Beck EC, Barolin GS: The effect of hypnotic suggestion on evoked potentials. *J Nerv Ment Dis* 1965; 140:154–161
21. Beck EC, Dustman RE, Beier EG: Hypnotic suggestions and visually evoked potentials. *Electroencephalogr Clin Neurophysiol* 1966; 20:397–400
22. Serafetinides EA: Electrophysiological responses to sensory

- stimulation under hypnosis. *Am J Psychiatry* 1968; 125:112-113
23. Zakrewski K, Szelenberger W: Visual evoked potentials in hypnosis: a longitudinal approach. *Int J Clin Exp Hypn* 1981; 29: 77-86
 24. Halliday AM, Mason AA: Cortical evoked potentials during hypnotic anaesthesia. *Electroencephalogr Clin Neurophysiol* 1964; 16:312-314
 25. Barabasz AF, Lonsdale C: Effects of hypnosis on P₃₀₀ olfactory-evoked potential amplitudes. *J Abnorm Psychol* 1983; 92:520-523
 26. Spiegel D, Barabasz AF: Effects of hypnotic instructions on P₃₀₀ event-related potential amplitudes: research and clinical implications. *Am J Clin Hypn* 1988; 31:11-17
 27. Spiegel D, Cutcomb S, Ren C, et al: Hypnotic hallucination alters evoked potentials. *J Abnorm Psychol* 1985; 94:249-255
 28. Hilgard ER, Hilgard JR: *Hypnosis in the Relief of Pain*. Los Altos, Calif, William Kaufmann, 1975
 29. Spiegel D, Bloom JR: Group therapy and hypnosis reduce metastatic breast carcinoma pain. *Psychosom Med* 1983; 45:333-339
 30. Kihlstrom JF: The cognitive unconscious. *Science* 1987; 237: 1445-1452
 31. Halliday AM: Commentary: evoked potentials in neurological disorders, in *Event-Related Brain Potentials in Man*. Edited by Callaway E, Tueting P, Koslow SH. New York, Academic Press, 1978
 32. Shor RE, Orne EC: *Harvard Group Scale of Hypnotic Susceptibility: Form A*. Palo Alto, Calif, Consulting Psychologists Press, 1959
 33. Weitzenhoffer AM, Hilgard ER: *Stanford Hypnotic Susceptibility Scale: Form C*. Palo Alto, Calif, Consulting Psychologists Press, 1962
 34. Spiegel H, Spiegel D: *Trance and Treatment: Clinical Uses of Hypnosis* (1978). Washington, DC, American Psychiatric Press, 1987
 35. Hansen JC, Hillyard SA: Endogenous brain potentials associated with selective auditory attention. *Electroencephalogr Clin Neurophysiol* 1980; 49:277-290
 36. Desmedt JE, Bourguet M, Huy NT, et al: The P₄₀ and P₁₀₀ processing positivities that precede P₃₀₀ closure in serial somatosensory decision tasks, in *Brain and Information: Event-Related Potentials*. Edited by Karper R, Cohen J, Tueting P. New York, New York Academy of Sciences, 1984
 37. Orne MT: The nature of hypnosis: artifact and essence. *J Abnorm Soc Psychol* 1959; 58:277-299
 38. Spiegel H: The grade 5 syndrome: the highly hypnotizable person. *Int J Clin Exp Hypn* 1976; 22:303-319
 39. Desmedt JE, Robertson D: Differential enhancement of early and late components of the cerebral somatosensory evoked potentials during fast sequential cognitive tasks in man. *Physiology* 1977; 27:761-782
 40. Josiassen RC, Shagass C, Roemer RA, et al: Somatosensory evoked potential changes with a selective attention task. *Psychophysiology* 1982; 19:146-159
 41. Schechter G, Buchsbaum M: Cognitive dissonance modifies somatosensory evoked potentials to experimental pain. *Society for Psychophysiological Research Abstracts* 1985; 22:612
 42. Buchsbaum MS, Davis GC: Application of somatosensory event related potentials to experimental pain and the pharmacology of analgesia, in *Human Evoked Potentials: Applications and Problems*. Edited by Lehmann D, Callaway E. New York, Plenum, 1979
 43. Hillyard SA, Squires KC, Bauer JW, et al: Evoked potential correlates of auditory signal detection. *Science* 1971; 172: 1357-1360
 44. Paul DD, Sutton S: Evoked potential correlates of response criterion in auditory signal detection. *Science* 1972; 177:362-364
 45. Davis GC, Buchsbaum MS, van Kammen DP, et al: Analgesia to pain stimuli in schizophrenics and its reversal by naltrexone. *Psychiatry Res* 1979; 1:61-69
 46. Goldstein A, Hilgard ER: Failure of opiate antagonist naloxone to modify hypnotic analgesia. *Proc Natl Acad Sci USA* 1975; 72:2041-2043
 47. Spiegel D, Albert LH: Naloxone fails to reverse hypnotic alleviation of chronic pain. *Psychopharmacology (Berlin)* 1983; 81: 140-143
 48. Clark WC: Sensory-decision theory analysis of the placebo effect on the criterion for pain and thermal sensitivity (d'). *J Abnorm Psychol* 1969; 74:363-371
 49. Goldberg E, Costa LD: Hemispheric differences in the acquisition and use of descriptive systems. *Brain Lang* 1981; 14:144-173
 50. Kinsbourne M: Hemisphere interactions in depression, in *Cerebral Hemisphere Function in Depression*. Edited by Kinsbourne M. Washington, DC, American Psychiatric Press, 1988
 51. Hilgard JR: *Personality and Hypnosis: A Study of Imaginative Involvement*. Chicago, University of Chicago Press, 1970

Physical and Sexual Assault Histories Among Psychiatric Outpatients

Andrea Jacobson, M.D., Ph.D.

Using a semistructured interview, the author obtained complete histories of experiences of being physically or sexually assaulted from 31 psychiatric outpatients. The majority (68%) of outpatients had experienced major physical and/or sexual assaults, and most assaults had not been revealed to the patients' prior therapists. Circumstances associated with the assaults, a comparison of outpatient and inpatient assault histories, and the relevance of the findings to clinical practice are discussed.

(Am J Psychiatry 1989; 146:755-758)

As the impact of having been sexually or physically assaulted becomes more widely recognized (1-3), it is important to know how widespread these experiences are among psychiatric patients. Physical and/or sexual assault prevalences for psychiatric inpatients have been reported to be as high as 43% in a chart review study (4) and as high as 70%-80% in direct interview studies (5, 6), but the prevalence of assault histories among outpatients remains unclear. The only study to my knowledge of a broad range of types of assault among psychiatric outpatients is a chart review (7) which reported that 22% of 105 outpatients had experienced physical or sexual violence. No direct interview studies surveying a broad range of assault experiences among outpatients have been reported.

Using a direct interview method developed in a prior study of inpatients (5), I conducted a study of physical and sexual assault histories among outpatients. I also compared assault prevalences among patients in two common treatment settings: inpatient units and a non-specialized general outpatient practice.

Received May 31, 1988; revision received Nov. 21, 1988; accepted Dec. 15, 1988. From the Department of Psychiatry and Behavioral Science, University of Washington, and the Department of Psychiatry, State University of New York at Buffalo. Address reprint requests to Dr. Jacobson, Department of Psychiatry and Behavioral Science, RP-10, University of Washington, Seattle, WA 98105.

Supported in part by Biomedical Research Support Grant 150-E-306N from NIH.

The author thanks Katherine Johnson-Kinniburgh and Jill Koehler for data collection and the outpatient and emergency room staff at Erie County Medical Center for assistance in subject recruitment.

Copyright © 1989 American Psychiatric Association.

METHOD

Patients were recruited at a large, university-affiliated county hospital. Because I was interested in the relevance of routine assault inquiry in a traditional, nonspecialized outpatient psychotherapy practice, I studied only new patients, excluding patients with chronic schizophrenia who were usually treated at multidisciplinary mental health centers and patients seen only for pharmacologic management. Therapists were requested to ask patients at the first meeting if they would be willing to meet with a research assistant who would tell them about a study of past experiences in which they could choose to participate. Of 123 eligible patients, 73 were approached by their therapists. Of these, 31 (42%) agreed to meet with a research assistant, who told them the exact nature of the study. No patients rejected the study at that stage. Five of the 31 patients initially came to the emergency room but were referred for outpatient treatment.

The median age of the 31 outpatients was 31 years (range, 19-75 years). The majority of subjects were either never married (N=13, 42%) or remarried (N=7, 23%), high school graduates (N=6, 19%) or partially college-educated (N=10, 32%), and clerical/sales workers (N=15, 48%) or unskilled/unemployed individuals (including housewives) (N=7, 23%). The majority of the sample (N=23, 74%) was white, and a substantial minority (N=8, 26%) was black; the predominant social classes (Hollingshead and Redlich) were class III (N=13, 42%) and class IV (N=11, 36%). Twenty-six (84%) of the subjects were women, and five (16%) were men. These outpatients were quite similar in median age, racial distribution, and marital status to the 100 previously studied inpatients. More of the outpatients, however, were women (84% versus 50%) and in a somewhat higher social class (predominantly classes III and IV versus predominantly classes IV and V).

The chart diagnoses of the outpatients included affective disorders (N=11, 36%), personality disorder and substance abuse (N=8, 26%), adjustment reaction (N=5, 16%), marital problems (N=2, 7%), and miscellaneous (N=5, 16%). This distribution was quite similar to the previous inpatient sample, except that none of the outpatients had diagnoses of schizophrenia

TABLE 1. Prevalence of Major Assault Histories Among 31 Psychiatric Outpatients and 100 Previously Studied Psychiatric Inpatients (5)

Type of Assault	Women				Men				All			
	Outpatient (N=26)		Inpatient (N=50)		Outpatient (N=5)		Inpatient (N=50)		Outpatient (N=31)		Inpatient (N=100)	
	N	%	N	%	N	%	N	%	N	%	N	%
Physical assault as child	9	35	22	44	3	60	27	54	12	38	49	49
Physical assault as adult	11	42 ^a	32	64 ^a	2	40	31	62	13	42 ^b	63	63 ^b
Sexual assault as child	11	42 ^c	11	22 ^c	1	20	8	16	12	38 ^d	19	19 ^d
Sexual assault as adult	10	38	19	38	0	0	2	4	10	32	21	21

^a $\chi^2=3.28$, $df=1$, $0.05 < p < 0.10$.

^b $\chi^2=4.31$, $df=1$, $p < 0.05$.

^c $\chi^2=3.43$, $df=1$, $0.05 < p < 0.10$.

^d $\chi^2=5.09$, $df=1$, $p < 0.05$.

or other psychosis and very few inpatients had adjustment reaction diagnoses.

The instrument and procedures were the same as those used and described in detail in the inpatient study (5). A lengthy semistructured interview was used to obtain history in four categories of assault: physical assault as a child, physical assault as an adult, sexual assault as a child, and sexual assault as an adult. Childhood included experiences that occurred before age 16; consensual sexual play between children of similar ages was not considered childhood sexual assault. Patients could describe up to four assault relationships (i.e., all assaultive acts of a specific category that the patient experienced with a specific assailant without regard for number of episodes or duration of relationship) in each category. Levels of severity were defined by detailed, behaviorally defined assault scales. Major sexual assault included sexual assault involving physical contact with the genitals of the victim, the assailant, or both. Major physical assault ranged in severity from "kick, bit, or hit" to "used a knife or gun." Patients who had experienced major assaults were also asked to identify specific characteristics of their assaults, such as alcohol or drug use by the assailant, patient, or both, maintenance of secrecy about the assault, perceived effects of the assault, and discussion of the assault in previous therapy. If a patient described more than one assault relationship in a specific category, the patient was asked to choose the most important and that assault relationship was then the subject of the more detailed inquiry. Data on less severe assault, such as exhibitionism, fondling, shoving, and throwing objects, are not presented. All the patients tolerated the interview well. Assistance in finding counseling to deal with any sequelae to the interview experience was offered but never used.

RESULTS

Histories of major physical and/or sexual assault were reported by 68% (N=21) of the outpatients. Of these 21 assaulted patients, 67% (N=14) had experienced more than one category of major assault and 10 (48%) had experienced three or all four categories.

Prevalence rates were calculated for each of the four assault categories (table 1). No sexual assault as an adult was reported by the men. Combined prevalences were 58% (N=18) for physical and/or sexual childhood assault, 48% (N=15) for physical and/or sexual adult assault, 61% (N=19) for childhood and/or adult physical assault, and 48% (N=15) for childhood and/or adult sexual assault.

The four categories of major assault were analyzed in pairs for occurrence in the same patient by using Fisher's exact test. Sexual assault as an adult tended to occur with both sexual assault as a child (N=7, $p < 0.02$) and physical assault as an adult (N=8, $p < 0.01$). The association of sexual and physical assault as an adult was largely explained by five women who reported being physically and sexually assaulted by the same man. Sexual assault as a child and physical assault as an adult tended to occur together (N=8, $p < 0.05$). No other significant associations between assault categories were noted, nor were there any associations between primary chart diagnoses and prevalence of assault. The demographic characteristics of the assaulted patients were similar to those of the total outpatient sample.

Table 2 illustrates how many of the 21 assaulted outpatients had ever experienced at least one assault (in any of the four major categories) with specific characteristics (e.g., an assault that recurred more than 20 times or an assault that had never been revealed to anyone). With respect to an association between each of these 11 characteristics and the four major categories of assault, some differences were found. Among 21 childhood or adult sexual assault relationships, 81% (N=17) were difficult for the patient to tell anyone about compared to 40% (N=8) of 20 childhood or adult physical assault relationships ($\chi^2=7.22$, $df=1$, $p < 0.01$). These 21 sexual assault relationships were also more likely to have been accompanied by major guilt (76%, N=14) than were the 20 physical assault relationships (45%, N=9), but the difference was only a statistical trend ($\chi^2=2.54$, $df=1$, $0.05 < p < 0.10$); however, major continuing effects were ascribed to more of the 20 physical assault relationships (70%, N=14) than to the 21 sexual assault relationships (43%, N=9), although the difference was only a sta-

TABLE 2. Specific Characteristics of Assaults Reported by 21 Psychiatric Outpatients and 81 Previously Studied Psychiatric Inpatients (5)

Assault Characteristic	Outpatients (N=21)		Inpatients (N=81)		χ^2 (df=1)
	N	%	N	%	
Occurred within 3 years before current hospitalization	7	33	39	48	—
Lasted at least 2 years	12	57	36	44	—
More than 20 episodes	12	57	40	49	—
Involved male assailant	20	95	78	96	—
Involved female assailant	10	48	20	25	4.22 ^a
Associated with alcohol or drugs ^b	12	57	41	51	—
Caused major guilt/shame at time ^b	18	86	53	65	3.24 ^c
Never revealed to anyone ^b	10	48	22	27	3.71 ^c
Not revealed to previous therapists ^b	15	71	40	49	3.26 ^c
Still causes major guilt/shame ^b	8	38	16	20	3.12 ^c
Self-reported continuing major effect on life	15	71	40	49	3.26 ^c

^a $p < 0.01$.^bOnly a subset of major assault relationships were examined with respect to these characteristics; therefore, these percentages underestimate the prevalence of exposure to assault associated with these characteristics.^c $0.05 < p < 0.10$.

tistical trend ($\chi^2=3.06$, $df=1$, $0.05 < p < 0.10$). There was a higher prevalence of the use of drugs or alcohol by assailant, victim, or both during 20 adult physical assault experiences (82%, $N=9$) than during 30 other assault experiences in the other three categories of assault (37%, $N=11$) ($\chi^2=7.77$, $df=1$, $p < 0.01$).

As shown in table 1, a lower percentage of outpatients than inpatients had experienced physical assault as an adult, but a higher percentage had histories of sexual assault as a child. There were no significant differences in either of the other two categories between inpatients and outpatients. A higher percentage of women outpatients than women inpatients had histories of sexual assault as a child and a lower percentage had histories of physical assault as an adult, but these differences were only trends; there were no significant differences between women outpatients and women inpatients in the other two categories of assault. Outpatient and inpatient prevalences for men could not be meaningfully compared because there were only five men in the outpatient sample. The inpatient and outpatient prevalences for most of the 11 different characteristics of assault were quite similar (table 2).

DISCUSSION

The majority (68%) of the outpatients interviewed had experienced major physical or sexual assault. This percentage is far higher than the 22% previously reported in a chart review study (7). Chart reviews can miss assault histories, either because the assault was not discussed during routine clinical treatment or because the assault was not recorded on the chart (8, 9).

Each of the four assault categories had been experienced by at least one-third of the sample. The length of assaultive relationships reported by these patients, the past and sometimes current guilt and shame, and the perceived continuing effects on life reveal that these assaults were major events in the patients' lives. How-

ever, the importance attributed to assaults by patients was sometimes surprising. One patient found her mother's breaking windows more disturbing than having her own bone broken. Another patient who had experienced forced genital touching and oral-genital sex with her stepfather for more than 5 years noted very little effect on her life. The psychological importance of assault needs to be understood from each patient's perspective, and the possibility of denial should be considered.

Sexual assault relationships were described by victims as being more difficult to reveal and more guilt-inducing at the time of occurrence than physical assault relationships but also as having less impact on their lives. This apparent paradox could be due to denial as well as to social stigma, both of which support the need for routine clinical inquiry about assault history (5) and for continuing alertness to clues of unrevealed assault history during outpatient treatment.

Our sample was relatively small and limited to new patients. A possible bias may have been introduced by the elimination of 41% of the eligible patients because of the therapists' failure to approach them about the study, although most of the reasons seemed unrelated to the subject of the research (forgot, did not want to interrupt the meeting, or were concerned about affecting the therapeutic relationship). All of the patients' refusals to participate occurred before they were told the specific subject of the study. The study interview did not inquire specifically about marital rape, which may be almost as prevalent among women as non-marital rape (10–12). In future studies, we recommend that spouses and lovers be specifically mentioned as possible assailants, to avoid underestimates of sexual abuse as adults. Despite these limitations, this direct interview study of psychiatric outpatients helps to fill a void in the literature on assault experiences.

There were remarkably few differences in prevalence of assault or associated characteristics between this outpatient sample and the prior inpatient sample. Although an association between both physical and sex-

ual assault histories and psychiatric symptoms has been repeatedly reported (3), I found no evidence that the presumably more disturbed inpatients had a higher percentage of assaultive experiences than the outpatients, except for a trend for women inpatients to have reported more physical assault as an adult.

A comparison of assault prevalences between psychiatric patients and the general population is difficult at this time. Recently, childhood sexual assault prevalences as high or higher than those reported in psychiatric samples have been obtained in general population surveys (13, 14). These studies, however, used longer interviews, multiple and sometimes overlapping screening questions, and highly trained interviewers, all factors that may be associated with higher disclosure of assault history (15); therefore, the data are not truly comparable. Available data thus far continue to suggest that physical assault histories are more common among psychiatric patients than in the general population, although the same problem of different methodologies remains (16, 17).

REFERENCES

1. Browne A, Finkelhor D: Impact of child sexual abuse: a review of the research. *Psychol Bull* 1986; 99:66-77
2. Herman J, Russell D, Trocki J: Long-term effects of incestuous abuse in childhood. *Am J Psychiatry* 1986; 143:1293-1296
3. Mullen PE, Romans-Clarkson SE, Walton VA, et al: Impact of sexual and physical abuse on women's mental health. *Lancet* 1988; 1:841-845
4. Carmen E(H), Rieker PP, Mills T: Victims of violence and psychiatric illness. *Am J Psychiatry* 1984; 141:378-383
5. Jacobson A, Richardson B: Assault experiences of 100 psychiatric inpatients: evidence of the need for routine inquiry. *Am J Psychiatry* 1987; 144:908-913
6. Bryer JB, Nelson BA, Miller JB, et al: Childhood sexual and physical abuse as factors in adult psychiatric illness. *Am J Psychiatry* 1987; 144:1426-1430
7. Herman JL: Histories of violence in an outpatient population: an exploratory study. *Am J Orthopsychiatry* 1986; 56:137-141
8. Jacobson A, Koehler JE, Jones-Brown C: The failure of routine assessment to detect histories of assault experienced by psychiatric patients. *Hosp Community Psychiatry* 1987; 38:386-389
9. Post RD, Willett AB, Franks RD, et al: A preliminary report on the prevalence of domestic violence among psychiatric inpatients. *Am J Psychiatry* 1980; 137:974-975
10. Russell DEH: Rape in Marriage. New York, Collier, 1982
11. Russell DEH: The prevalence and incidence of forcible rape and attempted rape of females. *Victimology* 1982; 7:81-93
12. Frieze IH: Investigating the causes and consequences of marital rape. *Signs* 1982; 8:532-553
13. Russell DEH: The incidence and prevalence of intra familial and extra familial sexual abuse of female children. *Child Abuse Negl* 1983; 7:133-146
14. Wyatt GE: The sexual abuse of Afro-American and white-American women in childhood. *Child Abuse Negl* 1985; 9: 507-519
15. Peters SD, Wyatt GE, Finkelhor D: Prevalence, in A Sourcebook on Child Sexual Abuse. Edited by Finkelhor D. Beverly Hills, Calif, Sage Publications, 1989
16. Straus MA, Gelles RJ, Steinmetz SK: Behind Closed Doors: Violence in the American Family. New York, Anchor/Doubleday, 1980
17. Straus M: Family patterns and child abuse in a nationally representative sample. *Child Abuse Negl* 1979; 3:213-225

Child Psychiatry Fellowship Training: A Crisis in Recruitment and Manpower

Eugene V. Beresin, M.D., and Jonathan F. Borus, M.D.

Eighty-three percent (104 of 126) of the accredited child psychiatry fellowships in the United States responded to a survey of current manpower and training problems facing child psychiatry. Thirty-five percent of the respondents were having trouble filling their classes with highly qualified fellows, and 45% were having difficulty recruiting faculty child psychiatrists. Other significant problems included developing faculty interest in research, providing didactic seminars in new areas such as developmental neurobiology and infant psychiatry, and funding fellow and faculty positions and research. The authors examine this crisis in manpower, recruitment, and training and suggest solutions on local and national levels.

(Am J Psychiatry 1989; 146:759-763)

There is currently a nationwide shortage of child psychiatrists. Although the Graduate Medical Education National Advisory Committee (GMENAC) predicted an overall surplus of physicians by 1990, it forecast a 20% shortage of general psychiatrists and a severe (45%) undersupply of child psychiatrists by that year (1). The GMENAC report has been criticized as inaccurate on a number of grounds (2, 3), and recent changes in the organization of health care delivery have led some to argue that the shortage of general psychiatrists predicted by GMENAC will not occur in the coming decade (3). Most experts agree, however,

that unless major changes are made, the current undersupply of child psychiatrists will continue into the next century.

In addition to concerns about quantity, there are also concerns about the quality of the child psychiatrists being produced in today's fellowship programs. These concerns are bolstered by the fact that almost one-third of the fellowship graduates who elect to take the child psychiatry Board examinations do not pass them (4). Although there are no recent studies beyond the Board pass rates assessing the quality of child psychiatry graduates, there are anecdotal data from child training directors about the poor quality of their applicants. Child training programs are also said to suffer from too few full-time faculty and an inadequate breadth of faculty expertise (5-7). Many programs are thought to not provide their trainees with fundamental knowledge and experience in new and exciting areas of the field (e.g., developmental neurobiology, genetics, epidemiology) (5, 7, 8). It has been suggested that the field thwarts its own advancement by paying inadequate attention to faculty development and isolating itself from general psychiatry and other areas of medicine (5, 7, 9).

Most of these concerns about the quantity and quality of child psychiatrists and child training programs remain opinions of the field's leaders and have not been supported by systematic research. The few noteworthy exceptions are Enzer's unpublished study of child psychiatry faculty vacancies, the trend data of the American Medical Association (AMA) on entry into child psychiatry (10, 11), and Weissman and Bashook's follow-up study of the interest of newly matched psychiatry residents (12, 13). In an unpublished national survey, sponsored by the Society of Professors of Child Psychiatry and the American Association of Chairmen of Departments of Psychiatry, Enzer found that in 1987 approximately 100 full-time equivalent child psychiatry faculty positions at 115

Received April 12, 1988; revision received Dec. 7, 1988; accepted Dec. 20, 1988. From the Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School. Address reprint requests to Dr. Beresin, Child Psychiatry Service, Ambulatory Care Center 625, Massachusetts General Hospital, Boston, MA 02114.

The authors thank Michael Jellinek for his guidance and comments on the manuscript and Debby Redifer and Suzanne Lacey for assistance in data collection.

Copyright © 1989 American Psychiatric Association.

TABLE 1. Trends in Recruitment of Child Psychiatry Fellows*

Year	Number of Approved Programs	Child Fellow Positions			American Medical Graduates		Foreign Medical Graduates	
		Offered	Filled		N	%	N	%
1976	134	696	564	81	384	68.0	180	32.0
1984	129	669	537	80	379	70.6	158	29.4
1985	128	665	580	87	420	72.4	160	27.6
1986	126	691	602	87	446	74.1	156	25.9

*Data are from references 10 and 11.

teaching institutions were funded but vacant. In comparing 1986 and 1976 figures, the AMA trend data (10, 11) reveal a 6% decrease in the number of accredited child psychiatry training programs and virtually no change in the number of training positions offered (table 1). These data also indicate that over this decade there has been a 6% increase in the number of positions filled and a 6.7% increase in the total number of child fellows in training. This discouraging upswing will only produce an additional 19 trained child psychiatrists a year, certainly not enough to avert the severe shortage of child psychiatrists predicted for the 1990s.

In one of the only empirical studies of resident entry into child psychiatry, Weissman and Bashook surveyed 59% (N=579) of the beginning residents who chose to specialize in psychiatry in the 1982 and 1983 national resident match (12, 13). They found that at the beginning of general psychiatry training there was significant interest in pursuing child psychiatry as a career, with 30% (N=173) of the residents indicating a plan to become child psychiatrists. These prospective child psychiatrists were indistinguishable from their resident peers as they entered residency, and the expectation of extending their training 1–2 years did not seem to diminish their interest in a child psychiatry career. However, when Weissman and Bashook followed up 33% (N=189) of their original subjects during the latter's PGY-4 year of training, they found that the number of residents who had actually entered child psychiatry in PGY-4 or planned to do so in PGY-5 had decreased from 30% to 18%. Among the small number of variables they studied, only a preference for working with children and a lack of interest in research distinguished those subjects still interested in child psychiatry from other PGY-4 psychiatry residents. Since the number of residents studied in the follow-up was small, the conclusions must be viewed with caution and do not provide sufficient data to fully explain what steered these residents away from child psychiatry.

In the report that follows we describe a survey of all accredited child psychiatry training programs in this country that was undertaken to provide a data-based nationwide picture of child psychiatry recruitment, training, and faculty. We then make recommendations for potential solutions to some of the problems in child psychiatry revealed by the survey.

THE SURVEY

Under the auspices of the Child Psychiatry Caucus of the American Association of Directors of Psychiatric Residency Training (AADPRT), a detailed survey was sent to all 126 accredited child psychiatry fellowship programs in the United States in the fall of 1986. The survey was addressed to child psychiatry training directors, and its stated intent was to assess the major areas of current difficulty in child psychiatry training and ways that the AADPRT could help find solutions to these difficulties. The instructions specified that all responses would remain confidential and that pooled data would be used only in AADPRT program and policy reviews and published reports.

The survey included demographic questions on each program's clinical base, funding sources, location, number of current fellows and faculty, and relationship to a general psychiatry training program. The main section asked the program directors about difficulties in recruiting highly qualified fellows and attracting faculty child psychiatrists; specific problems related to their program's didactic curriculum, core clinical rotations, professional development of the fellows, program evaluation, accreditation, and funding; difficulties in the relationship between child psychiatry and other medical specialties in their program; problems enhancing faculty development in research, supervision, and teaching; and difficulties they experienced learning effective skills as training directors. Questions were also raised about the organization of child psychiatry as a field, particularly whether program directors felt isolated and needed additional national forums for collaboration, education, and advocacy.

THE PROBLEMS

Eighty-three percent (N=104) of the accredited child psychiatry programs responded to the survey. Of the fellowship positions reported offered by the responding programs in 1986, 88% (505 of 576 positions) were filled, a finding similar to the AMA trend data previously cited. The vast majority of training programs were based in university medical schools or general hospitals and were located in urban centers with populations greater than 250,000. Programs were funded largely by three sources: university/medical school, state government, and private nonprofit hospitals, in that order. Seventy-nine percent had separate general and child psychiatry training programs in the same institution, 16% had a single, combined general and child psychiatry training program, and 5% had no general psychiatry program in their institution but were affiliated with an external general training program.

Recruitment of child psychiatry fellows was the most frequently noted problem in the survey. Fifty-three percent of the programs were having problems finding effective ways to recruit highly qualified fel-

lows, 35% were having troubles actually filling their classes with well-qualified trainees, and 68% requested AADPRT help with these issues.

Faculty recruitment and development represented the second most frequently noted problem. A large number of programs (45%) indicated they were having trouble recruiting faculty child psychiatrists, and 59% wanted AADPRT assistance in addressing this problem. Seventy-five percent of child psychiatry training programs had six or fewer full-time equivalent faculty members, close to one-third had only two to four full-time equivalent faculty members, and problems in faculty development were widespread. Forty-four percent of programs were having problems getting their faculty interested in doing research, 50% reported major problems teaching research skills to their fellows, and 59% requested help with this area. Another problem area was inadequate faculty expertise to teach a broad-based, didactic core curriculum to the fellows, and deficits were especially noted in newer content areas.

Funding of the training program and its fellows, faculty, and research was the third most frequently reported problem. Thirty-seven percent of programs indicated difficulties coping with changing economic and reimbursement policies, and 45% specifically requested help in learning to write effective training grant proposals as potential sources of new funding. Developing a comprehensive core didactic curriculum was the fourth most frequently noted problem. Approximately 45% of programs reported they could not adequately teach infant psychiatry and developmental neurobiology, while others noted areas of weakness including child psychopharmacology and behavior therapy. Ninety-two percent of programs requested access to course syllabi in such areas from other child psychiatry training programs to strengthen their didactic curriculum.

BEGINNING SOLUTIONS

The survey data both corroborate many speculations in the literature and substantiate concern about the future of child psychiatry. As expected, recruitment of a sufficient number of qualified trainees is seen as the number one problem, with fewer training positions being offered, 12% of those offered unfilled, and over one-third of program directors concerned about the quality of the fellows now filling their positions. What needs to be done to interest talented young physicians in child psychiatry, sustain that interest through general psychiatry training, and provide them with the broad-based training necessary to produce the higher quantity and better quality of child psychiatrists needed for the coming decades? In the remainder of this paper we will suggest some salient approaches to these problems.

The available data suggest that the first place to focus is on the general psychiatry department and its training program. If the 30% of all entering general psychiatry residents Weissman and Bashook found

planning to be child psychiatrists actually went into the field, they would more than fill the current number of child psychiatry training positions and make a major inroad into the shortage of child psychiatrists. However, something must happen during the initial years of general psychiatry training to cause the dramatic shift of interest away from child psychiatry by PGY-4.

One problem may be that interest in child psychiatry is not sufficiently nurtured during the early years of residency when the resident's psychiatric identity is beginning to develop. Most residents are not introduced to child psychiatry theory, patients, or faculty until PGY-3, and some do not work clinically with children until PGY-4. This late introduction to child work comes long after residents have been exposed to other exciting areas of psychiatry and have begun to bond with faculty mentors in these other areas. Many residents first see child psychiatry at a point in their residency when they are consolidating rather than expanding their professional identity. This problem is compounded by the fact that residents interested in PGY-4 child fellowships must begin the application process early in PGY-3, a time when they are just beginning their initial, often anxiety-provoking clinical exposure to children, adolescents, and families. They are often hesitant to make the career decision for child psychiatry and sign up for its extra period of training when they have inadequate clinical experience in the field. To alternatively postpone this choice and enter child psychiatry as a PGY-5 will add 2 more training years to their life, a commitment that many of today's residents shouldering large financial debts from medical school find difficult to accept.

We believe that exposure to child psychiatrists and child psychiatry theory and practice early in residency can help sustain the initial interest of residents who enter psychiatry planning a child psychiatry career. General training directors should identify these beginning residents and provide them with specific exposure to and nurturance by child psychiatry faculty. Many programs have a training supervisory or mentoring program in which a resident is assigned a specific faculty mentor to work with throughout training (14). Those residents with an initial interest in child psychiatry should be given a child psychiatrist as their mentor. In addition, a child psychiatrist should also be assigned as one of the supervisors of their beginning psychotherapeutic or psychopharmacologic work with inpatients or outpatients. This would not only introduce the resident to the usefulness of a developmental approach to understanding normal and pathological behavior in adults, but would also demonstrate that child psychiatrists are respected members of the general psychiatry department, with the implication that they also will be respected and still be part of psychiatry if they leave the residency to begin child psychiatry training.

A related second focus area is to provide all general psychiatry residents with early exposure to child psy-

chiatry theory and practice. It is easily argued that all general psychiatry residents would benefit from the developmental perspective which child psychiatrists can provide in understanding and helping change adult patients' pathological behaviors. Early clinical exposure to children would also help general psychiatry residents become aware of their patients' nonverbal behaviors and fantasies, areas more easily explored with children but relevant to understanding adults. In a truly general psychiatry training program, it makes pedagogical sense to initiate child and adolescent work near the beginning of training. The initial introduction of child psychiatry's anxiety-provoking learning demands to PGY-3 or PGY-4 residents centered on professional consolidation, autonomy, and separation may be counterproductive. Providing all general psychiatry residents with early exposure to child psychiatry would also help stimulate interest in child training for residents who had not initially had it in mind and would thereby increase the number going on to child fellowship.

We recognize that these suggestions present a dilemma for an already thinly stretched child psychiatry faculty now asked to devote a substantial amount of time and effort to general psychiatry residents. However, we strongly believe that without this input of child psychiatry faculty energy early in general psychiatry training, there will not be quality child psychiatry fellows to train. We emphasize this solution because we are impressed that if initial interest in child psychiatry could be better supported and sustained through general psychiatry training, and if additional residents became interested in child psychiatry through early exposure to it, the field's "manpower crisis" would greatly diminish in size and urgency.

Some authors have suggested that child psychiatry resources would be well used in identifying medical students interested in the field and stimulating their interest through exciting curricula and well-supervised clinical electives with children, adolescents, and families, by getting them involved with research in the field, and increasing the visible role of child psychiatrists in administrative positions in medical schools (2, 15). Other tacks include the significant presence of child psychiatrists as teachers and role models to pediatric house officers, whose initial specialty choice clearly demonstrates interest in children and who might wish to take child psychiatry training instead of, or after completing, full pediatric training. Although these are clearly important "fertile fields" for potential recruits to child psychiatry, the shortage of child psychiatry faculty in many programs makes such a broad-ranging effort impossible and, as stated earlier, we believe these efforts should clearly be secondary to a major emphasis on working with general psychiatry residents.

The success of these suggestions hinges to a great extent on the relationship between the department or division of child psychiatry and the general psychiatry department. It is easier to demonstrate to adult psychiatry residents, pediatric residents, and medical students that child psychiatry is a respected part of the

field when it is neither isolated nor belittled by the members of the general psychiatry department; when the chairpersons of psychiatry and child psychiatry work well together; and when the general and child training directors collaborate and share resources. In particular, the leaders of the general psychiatry department must give sufficient priority to child psychiatry training and regard it as worthy of energy, funding, and resources. Child psychiatry in many departments is viewed as just another subspecialization area clamoring for its piece of the departmental training pie. Some general training directors minimize the need for child training in general residency and view child psychiatry training primarily as a force that takes valuable senior residents away from their programs.

For its part, child psychiatry has to decrease its longstanding isolation from general psychiatry and the larger field of medicine. Child psychiatry must give up its tradition of training in separate community-based child guidance clinics and increase its collaborations with general psychiatry, pediatrics, and other departments in the academic medical center (9). Since 97 of the 104 programs in our survey were located in the same institution as a general psychiatry training program, collaboration through joint participation in clinical services, supervision, teaching, and research should be logistically feasible. This would help child psychiatry faculty feel more a part of academia, bring child psychiatry clinicians in closer contact with general residents, and open up opportunities for collaboration between child psychiatry faculty and others in the medical center. In many settings child psychiatry will have to take the first steps to prove its availability, interest, and usefulness to the general psychiatry department and others in the medical center, but this effort will provide child psychiatry with the access and credibility it needs to increase its recruitment and gain the vital support of the chair of general psychiatry.

All of these suggestions are dependent on the establishment and maintenance of sufficient numbers of high-quality faculty child psychiatrists to serve as role models and provide the teaching, clinical supervision, and research necessary for general residency and child fellowship training. Consistent with Enzer's findings, our survey revealed significant current problems in faculty recruitment and development. A problem with the data in our study is that shortages and faculty vacancies were expressed in terms of full-time equivalent faculty members. It is not clear how much time any faculty member actually spends in a program; i.e., four full-time equivalent faculty members could mean that there are a total of four faculty members in the department, a situation in which it is unlikely that the full range of academic child and adolescent psychiatry is represented, or it could represent the part-time efforts of many faculty members who together possess the expertise to teach and demonstrate a broad range of diverse subspecialty areas. In addition, we did not explore specifically how many of the faculty were non-psychiatrist mental health professionals (e.g., psychol-

ogists, social workers) or what areas of expertise were represented in each department's child psychiatry faculty. Further investigation of these measures of the adequacy of child psychiatry faculty is clearly needed.

How can the development of child psychiatry faculty be fostered? To become respected members of the general psychiatry department and the academic medical center, child psychiatry faculty must become more "academic" and involved in research about their field (6-8). In this regard, Weissman and Bashook's finding that there seemed to be little interest in research among PGY-4 residents planning careers in child psychiatry is ominous. Departments of psychiatry must increase the priority of and supports and incentives for child psychiatrists to learn to undertake productive research. For departments with a critical mass of researchers on their child psychiatry faculty, an introduction to child psychiatry research should begin during fellowship training, with required research seminars and opportunities to collaborate with faculty on research projects. Departments lacking child psychiatry researchers should initiate collaborations with general psychiatry investigators, adding child and adolescent components to existing projects. For example, in our department, longitudinal investigations of the psychobiology of depression in adults have been broadened to include developmental studies of the children of depressed parents and risk factors in families of depressed adults, fertile areas for the research participation of child psychiatry faculty and fellows. Similar collaborative opportunities exist with established pediatric investigators interested in exploring the multiple psychosocial aspects of childhood development and disease. Post-fellowship research training tracks in child psychiatry should be developed on a regional basis to perpetuate interest in child research; adequate funding for such post-fellowship research training is crucial, as lengthily trained child psychiatrists at some point need to be able to make a living and pay off debts incurred in their education.

The latter suggests that changes at the local level must be paralleled by greater support for child psychiatry at the national level. As important as National Institute of Mental Health (NIMH) faculty scholar awards in child psychiatry and the NIMH priority on children and youth for research and training funds in recent years have been, they are inadequate in scope and size to deal with the multiple needs of child psychiatry. Our survey found that the federal and for-profit sectors provide less than 20% of child psychiatry fellowship support. Collaboration among national organizations interested in improving child psychiatry manpower, clinical services, training, and research is essential in lobbying regional and national legislative bodies for increased financial support for child psychiatry. Such consortia should also work to stimulate greater involvement by the growing for-profit care sector in helping to pay for the training of the future child psychiatrists who will staff their delivery systems and for research that will define more effective treatment modes from which they will profit.

Such nationwide collaboration in child psychiatry has begun. A National Recruitment Conference in Child Psychiatry, under the consortial sponsorship of the American Academy of Child and Adolescent Psychiatry, the American Association of Chairmen of the Departments of Psychiatry, the APA, the Society of Professors of Child Psychiatry, the Association for Academic Psychiatry, and the AADPRT, was held in January 1989 to define priorities and a plan to improve child psychiatry recruitment and manpower. For the last 2 years a national child psychiatry training consortium has met annually to coordinate training activities and initiatives. At its 1988 annual meeting the American Academy of Child and Adolescent Psychiatry devoted a full day symposium to address issues of training general psychiatry residents and child fellows, and its training committee is working with the AADPRT and the Association for Academic Psychiatry to produce a library of core curricula in several areas of child psychiatry for use by fellowship training programs nationwide. These trends are encouraging, as only with greater collaboration at the local and national levels will child psychiatry gain the power to plan, lobby, and proactively strive to increase its support and the likelihood of its survival.

REFERENCES

1. Graduate Medical Education National Advisory Committee: Report to the Secretary, vols 1-7: Publication HRA 81-651-657. Washington, DC, US DHHS, 1980
2. Pardes H, Pincus HA: Report of the Graduate Medical Education National Survey Advisory Committee and health manpower development: implications for psychiatry. *Arch Gen Psychiatry* 1983; 40:97-102
3. Yager J, Borus JF: Are we training too many psychiatrists? *Am J Psychiatry* 1987; 144:1042-1048
4. Robinowitz CB: 1985 annual report of the American Board of Psychiatry and Neurology, Inc. *Am J Psychiatry* 1986; 143:1358-1360
5. Philips I, Cohen RL, Enzer NB: *Child Psychiatry: A Plan for the Coming Decades*. Washington, DC, American Academy of Child Psychiatry, 1983
6. Rutter M: "Project future": the way forward for child psychiatry? *J Am Acad Child Psychiatry* 1984; 23:577-581
7. Guze SB: Child psychiatry: taking stock. *Compr Psychiatry* 1983; 24:1-5
8. Rutter M: Child psychiatry: looking 30 years ahead. *J Child Psychol Psychiatry* 1986; 27:803-840
9. Earls F: The future of child psychiatry as a medical discipline. *Am J Psychiatry* 1982; 139:1158-1161
10. American Medical Association: *Directory of Accredited Residencies, 1977-1978*. Chicago, AMA, 1977
11. American Medical Association: *1987-1988 Directory of Graduate Medical Education Programs*. Chicago, AMA, 1987
12. Weissman SH, Bashook PG: Manpower and recruitment, in *Basic Handbook of Training in Child and Adolescent Psychiatry*. Edited by Cohen RC, Duncan MK. Springfield, Ill, Charles C Thomas, 1987
13. Weissman SH, Bashook PG: A view of the prospective child psychiatrist. *Am J Psychiatry* 1986; 143:722-727
14. Borus JF, Groves JE: Training supervision as a separate faculty role. *Am J Psychiatry* 1982; 139:1339-1342
15. Silver LB: The crisis in child psychiatry recruitment in the United States—circa 1980. *J Am Acad Child Psychiatry* 1980; 19:711-719

Clinical Predictors of Recurrence in Depression

Donna E. Giles, Ph.D., Robin B. Jarrett, Ph.D., Melanie M. Biggs, M.A.,
David S. Guzick, M.D., Ph.D., and A. John Rush, M.D.

In a longitudinal study of 30 successfully treated unipolar depressed patients, the authors evaluated number of depressive episodes, early onset of depression, and lifetime prevalence of affective disorders other than major depression as risk factors for recurrence. Early onset of depression (before age 20) and a history of affective disorders other than major depression were each significantly associated with recurrence. Number of episodes was not as powerful in predicting recurrence as either early onset or lifetime prevalence of other affective disorders.

(Am J Psychiatry 1989; 146:764-767)

The episodic course of depression is well recognized clinically and has been documented in many studies (1-5). Factors reported to influence recurrence have included history of depressive episodes (6, 7), age at onset (8), clinical features (9, 10), treatment type (11-15), and latency before the first REM sleep period (16). Because several factors are associated with the course of depression, a multifactorial model in the systematic longitudinal assessment of biological, psychological, and clinical functioning of depressed patients during, after, and before episodes of depression seemed warranted.

Presented in part at the 26th annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, Dec. 7-11, 1987. Received June 6, 1988; revision received Nov. 22, 1988; accepted Dec. 15, 1988. From the Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas. Address reprint requests to Dr. Giles, Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213.

Supported by NIMH grants MH-35370, MH-39531, MH-41115, and MH-38238 and by NIH grant 1RR-00633.

The authors thank R. Boyer, M.S.W., G.G. Eaves, Ph.D., M. Khattami, M.D., D. Tyler, M.D., N. Vasavada, M.D., T.C.R. Wilkes, M.B., and J.K. Witschy, M.D., for clinical support.

Copyright © 1989 American Psychiatric Association.

We have evaluated at monthly intervals after successful treatment a group of patients with unipolar depression. Monthly documentation of clinical, biological, and psychological functioning provides refined assessment of factors associated with recurrence and of subsyndromal disturbances in these patients. Previously, we (16) found that short REM latency before treatment was associated with a high likelihood of recurrence and with a short time to recurrence. We have followed an expanded sample of patients for up to 3 years. Results of several studies (1, 3, 5) have indicated that a history of depressive episodes is the best predictor of recurrence. In this report, we present preliminary findings regarding early onset of depression, lifetime prevalence of affective disorders other than major depression, and history of depressive episodes as risk factors for recurrence.

METHOD

Successfully treated patients who met Research Diagnostic Criteria (RDC) (17) for major depressive disorder, unipolar type, before treatment were evaluated at monthly intervals after treatment. Criteria for successful treatment included 1) absence of DSM-III axis I or RDC disorders, 2) Hamilton Rating Scale for Depression (18) scores of 10 or lower, and 3) persistent remission for at least 8 weeks. All patients were studied at the Affective Disorders Unit, University of Texas Southwestern Medical Center, Dallas. Informed consent was obtained before treatment was initiated, after the evaluation and treatment procedures had been explained.

Detailed information regarding family history of psychiatric illness, age at onset of major depression, number of depressive episodes, presence or absence of concurrent and previous affective disorders other than major depression, and history of nonaffective disorders were gathered by using the Schedule for Affective Dis-

orders and Schizophrenia—Lifetime Version (19) and clinical interviews. Patients with current substance abuse, organic affective disorder, psychotic depression, recent suicide attempts, and major medical illnesses were excluded.

Of the 30 unipolar patients eligible for this study, 18 were women and 12 were men. Virtually all (93.3%) had primary depression. Their mean \pm SD age was 41.7 ± 11.7 years (range, 24–64 years). Their mean \pm SD Hamilton depression scale score was 19.2 ± 5.2 . Most patients (24 of 30 or 80%) had had onset of depression before age 40, and six (20%) had had onset of depression before age 20. Twenty-three patients (76.7%) had had at least two episodes of depression, and 14 (46.7%) had had three or more episodes. Two-thirds (N=20) had at least one family member with depression. Nine patients (30%) reported having had another affective disorder in addition to major depressive disorder: seven (23.3%) reported a history of intermittent depressive disorder, and two (6.7%) reported a history compatible with labile personality.

Twenty-nine of the 30 patients received either tricyclic antidepressant medication for 6 ± 1 months (N=20) or cognitive therapy (20) for 4 months (N=9). One patient, who had had five episodes of depression, received no formal treatment but recovered spontaneously during assessment. Medication-treated patients were monitored weekly for 6–8 weeks and monthly thereafter. All the drug-treated patients had blood drawn to determine plasma antidepressant levels at each visit and were within therapeutic range throughout treatment. By protocol, the patients who received cognitive therapy were seen for 20 sessions: twice a week for the first 6 weeks and on a more flexible schedule thereafter. All therapists were experienced and specifically trained in cognitive therapy. None of the patients received pharmacotherapy or psychotherapy in the posttreatment assessment period.

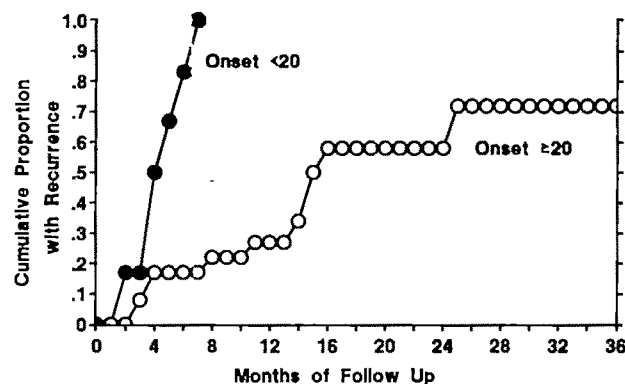
RESULTS

The 30 successfully treated patients were evaluated at monthly intervals for up to 36 months. During this follow-up period, 17 (56.7%) developed another episode of depression. Life table analysis (21) was used to accommodate varying follow-up intervals and the fact that risk of recurrence is not constant for all patients at all assessment points (22). A Lee-Desu (23) chi-square procedure was used to compare life table curves.

Life table analyses were done comparing 1) patients with one or two depressive episodes to those with three or more episodes ($\chi^2=1.70$, $df=1$, $p=0.19$), 2) patients with one episode to those with three or more episodes ($\chi^2=0.20$, $df=1$, $p=0.66$), and 3) patients with one episode to those with four or more episodes ($\chi^2=0.22$, $df=1$, $p=0.64$). None of these comparisons was associated with differences in recurrence rates.

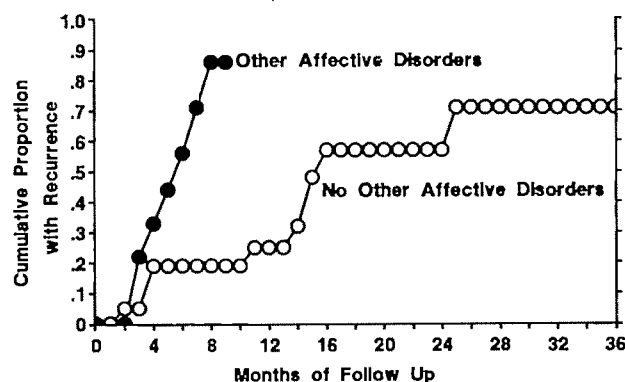
The life table curves comparing patients with early onset of depression (before age 20) to those with later

FIGURE 1. Life Table Analysis (21) of Recurrence of Depression in Six Patients With Early Onset (Before Age 20) and 24 With Later Onset (Age 20 or After)^a



^aSignificantly greater likelihood of recurrence in patients with early onset ($\chi^2=9.46$, $df=1$, $p=0.002$).

FIGURE 2. Life Table Analysis (21) of Recurrence of Depression in Nine Patients With and 21 Without a History of Affective Disorder Other Than Major Depression^a



^aSignificantly greater likelihood of recurrence in patients with a history of another affective disorder ($\chi^2=5.77$, $df=1$, $p=0.02$).

onset (age 20 or after) indicated that early onset was associated with a significantly greater likelihood of recurrence (figure 1). To determine whether factors other than early onset influenced recurrence rates, we compared these two groups on variables associated with recurrence. Age at evaluation ($t=1.55$, $df=28$, $p=0.13$), severity of depression ($t=0.59$, $df=28$, $p=0.56$), number of episodes of depression (Welch's $t=2.22$, $df=4.5$, $p=0.08$), history of intermittent depressive disorder and labile personality ($\chi^2=0.49$, $df=1$, $p=0.49$), history of nonaffective disorders ($\chi^2=0.23$, $df=1$, $p=0.63$), and family history of depression ($\chi^2=0.23$, $df=1$, $p=0.63$) were comparable for both groups.

Life table curves for the nine patients with a history of affective disorder other than major depression (intermittent depressive disorder, N=7; labile personality, N=2) and the 21 patients without such a history indicated that those with a history of another affective

disorder were at significantly higher risk for recurrence (figure 2). These groups did not differ with respect to age at evaluation ($t=0.10$, $df=28$, $p=0.92$), number of depressive episodes ($t=0.13$, $df=26$, $p=0.90$), age when first depressed ($t=0.66$, $df=28$, $p=0.52$), history of nonaffective disorders ($\chi^2=0.00$, $df=1$, $p=1.0$), and family history of depression ($\chi^2=0.18$, $df=1$, $p=0.67$). Patients with a history of other affective disorders had lower Hamilton depression scale scores at initial evaluation than those without such a history (16.3 ± 2.2 and 20.4 ± 5.6 , respectively; Welch's $t=2.87$, $df=27.9$, $p=0.01$).

DISCUSSION

Although the number of patients in this study is relatively small, these data can provide meaningful, albeit cautious, evaluation of factors influencing recurrence. Our patients were homogeneous with regard to several factors that influence recurrence of depression (24). None of our patients had chronic medical disorders, serious suicide attempts, or psychotic depression. Most had a family history of depression.

Contrary to research in this area (1, 5) and to clinical experience in general, number of depressive episodes was not predictive of recurrence. This finding may be due to the fact that most of our patients had recurrent depression or to the follow-up period of 36 months, a relatively short period in the natural course of depression. However, early onset of depression and lifetime prevalence of other affective disorders superseded history of depressive episodes as factors influencing recurrence. These factors may independently contribute to number of lifetime episodes, a possibility that has not been directly assessed. Early onset of depression (before age 20) has been associated with a high risk for depression among family members (25, 26) but to our knowledge has not been empirically associated with a high likelihood of recurrence. The association between a history of affective disorders other than major depression and a high likelihood of recurrence cannot be explained by persistent symptoms after treatment since patients were in complete remission at the time that follow-up began. Previous research (27) found that concurrent affective illnesses (major depression and dysthymic disorder) have been associated with recurrence. Although we evaluated lifetime prevalence of other affective disorders rather than concurrent affective disorders, we still found that patients with a complex history of affective disorder had a greater risk of recurrence than those without such a history.

Our sample size prohibits meaningful evaluation of the interactive or additive effects of early onset of depression and a history of chronic subsyndromal affective disorders. To the extent that we controlled statistically for confounding factors, we suggest that these factors are operating independently. The preeminence of early onset of depression and lifetime prevalence of

other affective disorders as influences on recurrence is intriguing and could tentatively suggest that number of depressive episodes per se is a function of a biologically or psychologically compromised substrate associated with the effects of developing the illness in the formative years and/or with chronic, although not unrelenting, subsyndromal affective disturbance.

Our patients were at a high risk for depression by virtue of their positive family history. Developmental or maturational processes may be further impaired by early or sustained affective disturbance, such that the basis for maintaining health has been weakened or the threshold for developing depression has been lowered. Investigation of a larger independent sample of longitudinally studied depressed patients could provide a hypothesis-testing mechanism to evaluate more fully the validity of these risk factors and their potential interaction.

REFERENCES

1. Fieve RR, Platman SR, Plutchik RR: The use of lithium in affective disorders, II: prophylaxis of depression in chronic recurrent affective disorder. *Am J Psychiatry* 1968; 125:492-498
2. Coppen A, Noguera R, Bailey J, et al: Prophylactic lithium in affective disorders. *Lancet* 1971; 8:275-279
3. Angst J, Bastrup P, Grof P, et al: The course of monopolar depression and bipolar psychoses. *Psychiatr Neurol Neurochir* 1973; 76:489-500
4. Glen AIM, Johnson AL, Shephard M: Continuation therapy with lithium and amitriptyline in unipolar depressive illness: a randomized double-blind controlled trial. *Psychol Med* 1984; 14:37-50
5. Prien RF, Kupfer DJ, Mansky PA, et al: Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium-carbonate-imipramine combination. *Arch Gen Psychiatry* 1984; 41:1096-1104
6. Shapiro RW, Keller MB: Initial 6-month follow-up of patients with major depressive disorders: a preliminary report from the NIMH Collaborative Study of the Psychobiology of Depression. *J Affective Disord* 1981; 3:205-209
7. Keller MB, Shapiro RW, Lavori PW, et al: Relapse in major depressive disorder: analysis with the life table. *Arch Gen Psychiatry* 1982; 39:911-915
8. Grof P, Angst J, Haines T: The clinical course of depression: practical issues, in *Classification and Prediction of Outcome of Depression*. Edited by Schattauer FK. New York, Springer-Verlag, 1974
9. Klerman GL: Long-term treatment of affective disorders, in *Psychopharmacology: A Generation of Progress*. Edited by Lipton MA, DiMascio A, Killam KF. New York, Raven Press, 1978
10. Keller MB, Shapiro RW: "Double depression": superimposition of acute depressive episodes on chronic depressive disorders. *Am J Psychiatry* 1982; 139:438-442
11. Quitkin F, Rifkin A, Klein DF: Prophylaxis of affective disorders: current status of knowledge. *Arch Gen Psychiatry* 1976; 33:337-341
12. Kovacs M, Rush AJ, Beck AT, et al: Depressed outpatients treated with cognitive therapy or pharmacotherapy: a one-year follow-up. *Arch Gen Psychiatry* 1981; 38:33-39
13. Blackburn IM, Euson KM, Bishop S: A two-year naturalistic follow-up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. *J Affective Disord* 1986; 10:67-75
14. Prien RF, Kupfer DJ: Continuation drug therapy for major depressive episodes: how long should it be maintained? *Am J Psychiatry* 1986; 143:18-23

15. Simons AD, Murphy GE, Levine JL, et al: Cognitive therapy and pharmacotherapy for depression: sustained improvement over one year. *Arch Gen Psychiatry* 1986; 43:43-48
16. Giles DE, Jarrett RB, Roffwarg HP, et al: Reduced REM latency: a predictor of recurrence in depression. *Neuropsychopharmacology* 1987; 1:33-39
17. Spitzer RL, Endicott J, Robins E: Clinical criteria for psychiatric diagnosis and *DSM-III*. *Am J Psychiatry* 1975; 132:1187-1192
18. Hamilton M: Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1976; 6:278-296
19. Spitzer RL, Endicott J: *Schedule for Affective Disorders and Schizophrenia—Lifetime Version*, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1979
20. Beck AT, Rush AJ, Shaw BF, et al: *Cognitive Therapy of Depression*. New York, Guilford Press, 1979
21. Berkson J, Gage R: Calculation of survival rates for cancer. *Mayo Clin Proc* 1950; 25:270
22. Lavori PW, Keller MB, Klerman GL: Relapse in affective disorders: a reanalysis of the literature using life table methods. *J Psychiatr Res* 1984; 18:13-25
23. Lee E, Desu M: A computer program for comparing k samples with right-censored data. *Comput Programs Biomed* 1972; 2: 315-321
24. Consensus Development Panel: NIMH/NIH Consensus Development Conference Statement: mood disorders: pharmacologic prevention of recurrences. *Am J Psychiatry* 1985; 142:469-476
25. Weissman MM, Wickramaratne P, Merikangas KR, et al: Onset of major depression in early adulthood. *Arch Gen Psychiatry* 1984; 41:1136-1143
26. Price RA, Kidd KK, Weissman MM: Early onset (under age 30 years) and panic disorder as markers for etiologic homogeneity in major depression. *Arch Gen Psychiatry* 1987; 44:434-440
27. Keller MB, Lavori PW, Endicott J, et al: "Double depression": two-year follow-up. *Am J Psychiatry* 1983; 140:689-694

Treatment of Body-Dysmorphic Disorder With Serotonin Reuptake Blockers

Eric Hollander, M.D., Michael R. Liebowitz, M.D., Ronald Winchel, M.D.,
Almuth Klumker, M.D., and Donald F. Klein, M.D.

The authors describe five patients with body-dysmorphic disorder who responded preferentially to serotonin reuptake blockers. They review the literature, describe how patients with excessive concern about body abnormalities lie along a spectrum of doubt and certainty, and discuss similarities and differences between this disorder and obsessive-compulsive disorder.

(Am J Psychiatry 1989; 146:768-770)

The essential feature of body-dysmorphic disorder, a new diagnosis classified as a somatoform disorder in *DSM-III-R*, is preoccupation with some imagined defect in appearance in a normal-appearing person. Common complaints involve facial flaws. Even slight physical anomalies produce excessive concern. The belief in the defect is not of delusional intensity, as in delusional disorder, somatic subtype, and it does not occur exclusively during the course of anorexia nervosa or transsexualism. Body-dysmorphic disorder had been called dysmorphophobia and classified in *DSM-III* as an atypical somatoform disorder. It has also been called monosymptomatic hypochondriasis.

The difference between body-dysmorphic disorder and delusional disorder, somatic subtype, depends on whether the thoughts of a defect in appearance represent an overvalued idea (with uncertainty) as in dysmorphophobia (1) or reach delusional intensity (with certainty) as in monosymptomatic hypochondriacal psychosis (2). However, some feel that dysmorphophobia and monosymptomatic hypochondriasis are two different disorders (3, *DSM-III-R*), and some suggest that they are two variants of the same disorder (4).

We present five cases of body-dysmorphic disorder, describe the patients' symptoms and treatment re-

sponse to serotonin reuptake blockers, and discuss the similarities and differences between this disorder and obsessive-compulsive disorder.

CASE REPORTS

Case 1. Ms. A, a 25-year-old white woman, came for treatment shortly after getting married and graduating from law school. She believed that vascular markings on her nose made her unattractive and was fearful that they would expand to cover her face, causing her husband to leave her. She used make-up to cover the imagined defect, avoided mirrors, and made multiple visits to dermatologists and plastic surgeons. She exhibited no vegetative symptoms of major depression, but she was demoralized. After treatment with imipramine (150 mg/day), her outlook improved and she became less preoccupied with thoughts of her vascular markings. However, after looking in the mirror on one occasion while not wearing make-up, she deteriorated and her overvalued belief developed into delusional certainty about the vascular markings. The addition of pimozide (2 mg/day) was effective for 2 months in altering this delusional certainty to an uncertainty. Nevertheless, overvalued concern about her face persisted, and she developed new obsessional fears about possible damage to future babies as a result of the medication. After an increase in imipramine to 300 mg/day failed to result in additional improvement, Ms. A agreed to a trial of fluoxetine, a selective serotonin (5-HT) reuptake inhibitor reported effective in the treatment of obsessive-compulsive disorder (5). Pimozide and imipramine were discontinued, and 6 weeks after receiving fluoxetine, 80 mg/day, Ms. A reported a dramatic improvement in her overvalued concern about facial defects. She was able to resume socializing, made plans to resume her career, and overcame her avoidance of agents that could potentially harm her skin, such as sun and wind. She has continued fluoxetine therapy for 5 months, and her condition continues to improve. She has a clear family history of obsessive-compulsive disorder; her sister has classic obsessions and compulsions regarding contamination and fears exposure of radiation to her family. Her father, a successful businessman, has subclinical symptoms of obsessive-compulsive disorder, such as the need for symmetry and overconcern about the health of his children, but his symptoms are ego syntonic and do not interfere with his functioning.

Case 2. Mr. B, a 20-year-old single white man with a history of two previous psychiatric hospitalizations for "delusional depressions," developed the delusional belief during

Received March 31, 1988; revision received Aug. 1, 1988; accepted Dec. 15, 1988. From the Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, and the New York State Psychiatric Institute. Address reprint requests to Dr. Hollander, New York State Psychiatric Institute, 722 West 168th St., New York, NY 10032.

Supported in part by NIMH Research Scientist Development Award MH-00750 (Dr. Hollander).

Copyright © 1989 American Psychiatric Association.

these episodes that his face looked pale and his cheekbones were misshapen. He was treated with two series of ECT and various neuroleptics and antidepressants but experienced only partial response. After treatment with imipramine (300 mg/day), lithium (900 mg/day), and thioridazine (100 mg/day), he continued to have this delusional belief and believed that other young people would not want to associate with him because of his appearance. After discontinuing imipramine, a 5-week trial of 300 mg/day of clomipramine, a potent 5-HT reuptake blocker, effective in obsessive-compulsive disorder (6, 7), was instituted. Mr. B stopped believing that his facial appearance was abnormal, and his social functioning improved. Even though this improvement continued during 4 months of follow-up treatment with clomipramine, he still has depressive episodes. Mr. B's mother has a history of bipolar affective disorder and paranoid disorder.

Case 3. Mr. C, a 56-year-old married white man, has a history of recurrent unipolar depression that began at age 20. After a stressful incident at school at age 16, he began to worry that his nose was misshapen. His worry diminished after he had four separate rhinoplasty operations, but over the next several years, he became concerned about his thinning hair. From age 20 to age 50, his concerns about cosmetic deformity focused on different parts of his body at different times, including hairline, waist, and shoulders, and occurred either independently or concomitantly with episodes of major depression. Treatments included ECT, insulin coma therapy, psychotherapy, neuroleptics, tricyclics, and monoamine oxidase inhibitors (MAOIs), and he experienced partial remissions. At age 50 he became overwhelmed with the fear that his shoulders were severely sloped and appeared cachectic. He began lifting weights, performing innumerable push-ups, and constantly checking his appearance in the mirror. Treatment with two courses of ECT and follow-up treatment with lithium, alprazolam, and trazodone failed to improve his condition. At age 55, clomipramine was substituted for trazodone. Two weeks after receiving 100 mg/day of clomipramine, he had a remarkable remission from all symptoms of body-dysmorphic disorder and depression. He became increasingly social at work and home and admitted that his previous worries about his shoulders were unfounded. This improvement persisted for 8 months of follow-up treatment with clomipramine. There is a strong history of affective disorder in Mr. B's family.

Case 4. Ms. D, a 38-year-old married white woman, believed that her hair did not look right because it was not symmetric. She would spend up to 8 hours a day cutting each hair so that her hair was symmetric and "just so." Her feelings of uncertainty about her hair were followed by considerable anxiety, which resulted in her stopping whatever she was doing to pull out a mirror and start cutting her hair. This behavior had been present for 8 years, resulting in considerable marital and job stress, a feeling of demoralization, and very short hair. Ms. D began a double-blind trial of clomipramine. After 12 weeks of placebo treatment, her obsessional concern about her hair or her levels of anxiety and depression did not diminish. She was then treated openly with 200 mg/day of clomipramine; 6 weeks later and during 4 months of follow-up treatment with clomipramine, her overconcern about her hair abated and her levels of anxiety and depression lessened.

Case 5. Mr. E, a 24-year-old single white man, had a history of impulsive behavior, outbursts of anger, fear of

rejection, and separation anxiety as a child and received a provisional diagnosis of minimal brain dysfunction. As an adolescent he had two long-term hospitalizations, was treated with neuroleptics, and received diagnoses of borderline personality disorder, Tourette's syndrome, obsessive-compulsive disorder, and marijuana abuse. He had depressive episodes and panic attacks that were treated successfully with amitriptyline (100 mg/day) but resulted in impotence, which made him fearful of becoming homosexual. At age 20, while living with a girlfriend, he began to obsess and ruminate about his nose and penis. He believed that his penis was small and ugly. At age 21 he was treated with clomipramine, 60 mg/day, which relieved the obsessive thoughts about his penis. For the next 3 years, these thoughts ceased while he was taking clomipramine but returned when he intermittently discontinued the clomipramine. When smoking marijuana but not taking clomipramine, his overvalued thoughts of having a small penis would become delusional. At age 24, he was switched to fluoxetine, which was also effective; however, the fluoxetine was discontinued after he developed a skin rash, and his obsessive thoughts about this bodily abnormality returned. He was then switched back to clomipramine, 60 mg/day, and the body-dysmorphic symptoms again improved. Mr. E's mother suffers from obsessive-compulsive disorder.

DISCUSSION

All five patients had circumscribed thoughts about bodily defects that were out of proportion to any real abnormality. The body-dysmorphic symptoms, previously refractory to a variety of somatic treatments, substantially improved in each patient after treatment with serotonin reuptake blockers. One patient improved after treatment with two different serotonin reuptake blockers.

Previous case reports have documented some improvement in monosymptomatic hypochondriasis and dysmorphophobia after tricyclic antidepressant (8) and MAOI (9) treatment and in monosymptomatic hypochondriacal psychosis after pimozide (2). This is the first report to our knowledge of preferential response to agents that manifest potent serotonin reuptake blockade.

Four of the five patients had failed to respond to previous vigorous therapeutic trials with agents that have some serotonergic action, such as tertiary amine tricyclics, trazodone, and lithium. Nevertheless, all responded to the potent serotonin reuptake blockers fluoxetine and/or clomipramine, suggesting a potent 5-HT effect or a differential mechanism of action of these agents. We have reported (10) that agents selective for specific serotonin receptors may have different behavioral effects than nonspecific serotonergic agents. The fact that clomipramine and fluoxetine have selective antiobsessional effects in obsessive-compulsive disorder (5-7) raises the possibility of a common pathogenesis between body-dysmorphic and obsessive-compulsive disorders but does not exclude a possible antidepressant effect of these agents or a relationship between affective illness and body-dysmorphic disorder.

DSM-III-R defines obsessive-compulsive disorder as the presence of either obsessions or compulsions that cause marked distress, are time consuming, or significantly interfere with functioning. Obsessions are defined as "persistent ideas, thoughts, impulses, or images that are experienced, at least initially, as intrusive and senseless." Although this definition could include patients with body-dysmorphic disorder, several of our body-dysmorphic patients experienced their overvalued beliefs as ego syntonic rather than ego dystonic, and obsessive-compulsive disorder is typically but not always characterized by ego-dystonic obsessions.

A review and phenomenological analysis of obsessive-compulsive disorder (11) suggest that delusions can arise in the course of this illness. These delusions do not signify a schizophrenic diagnosis but represent generally transient, reactive affective or paranoid psychoses. The authors argue that obsessive-compulsive disorder represents a psychopathological spectrum along a continuum of insight and that patients at the extreme end have an obsessive-compulsive psychosis. We offer the same argument for body-dysmorphic disorder; i.e., patients at the extreme end (certainty), currently classified as having delusional disorder, somatic subtype, or as hypochondriacal psychosis, have body-dysmorphic psychosis. Phenomenologically, there may be a spectrum, but additional biological mechanisms may occur when patients reach the delusional end and concerns become fixed beliefs, which may explain the partial efficacy in case 1 of pimozide, a dopamine receptor blocker, in changing certainty to uncertainty.

First-degree relatives of patients with obsessive-compulsive disorder have been reported to have a higher than normal rate of obsessional traits (12). Two of our five patients had a family history of obsessive-compulsive disorder, but two also had a family history of affective disorder; thus, a genetic association in obsessive-compulsive disorder is not clear cut.

Patients with obsessive-compulsive disorder are felt to manifest abnormality of central serotonergic function on the basis of pharmacological response (6, 7) and cerebrospinal fluid (13) and peripheral platelet (14) findings. Furthermore, administration of oral *m*-chlorophenylpiperazine, a selective 5-HT agonist, has been shown to exacerbate obsessive-compulsive symptoms transiently (10, 15). If body-dysmorphic disorder patients respond preferentially to serotonin reuptake inhibitors, their response is consistent with possible serotonergic dysregulation. Mr. E manifested exacerbation of body-dysmorphic symptoms of delusional intensity while smoking marijuana, which has central 5-HT effects; however, this was not a selective 5-HT-provocative test, since marijuana affects several other

neurotransmitter systems, including acetylcholine. A case report (16) of a woman who developed body-dysmorphic disorder after chronic abuse of cyproheptadine, a serotonin antagonist, makes a serotonergic etiology intriguing.

Our findings suggest that agents with potent serotonin reuptake blockade, such as clomipramine and fluoxetine, may be the treatment of choice in body-dysmorphic disorder. Possible overlap of body-dysmorphic and obsessive-compulsive disorders remains unresolved and should be addressed in future studies.

REFERENCES

1. Thomas CS: Dysmorphophobia: a question of definition. *Br J Psychiatry* 1984; 144:513-516
2. Munro A, Chmara J: Monosymptomatic hypochondriacal psychosis: a diagnostic checklist based on 50 cases of the disorder. *Can J Psychiatry* 1982; 27:374-376
3. Thomas CS: Dysmorphophobia and monosymptomatic hypochondriasis (letter). *Am J Psychiatry* 1985; 142:1121
4. Brotman AW, Jenike MA: Reply to CA Thomas: Dysmorphophobia and monosymptomatic hypochondriasis (letter). *Am J Psychiatry* 1985; 142:1121
5. Fontaine R, Chouinard G: An open clinical trial of fluoxetine in the treatment of obsessive compulsive disorder. *J Clin Psychopharmacol* 1986; 6:98-101
6. Thoren P, Asberg M, Cronholm B, et al: Clomipramine treatment of obsessive compulsive disorder: a controlled clinical trial. *Arch Gen Psychiatry* 1980; 37:1281-1289
7. Insel TR, Murphy DL, Cohen RM, et al: Obsessive compulsive disorder: a double blind trial of clomipramine and clorgyline. *Arch Gen Psychiatry* 1983; 40:605-612
8. Brotman AW, Jenike MA: Monosymptomatic hypochondriasis treated with tricyclic antidepressants. *Am J Psychiatry* 1984; 141:1608-1609
9. Jenike MA: A case report of successful treatment of dysmorphophobia with tranylcypromine. *Am J Psychiatry* 1984; 141:1463-1464
10. Hollander E, Fay M, Cohen B, et al: Serotonergic and noradrenergic function in obsessive-compulsive disorder: behavioral findings. *Am J Psychiatry* 1988; 145:1015-1017
11. Insel TR, Akiskal HS: Obsessive-compulsive disorder with psychotic features: a phenomenologic analysis. *Am J Psychiatry* 1986; 143:1527-1533
12. Carey G, Gottesman II: Twin and family studies of anxiety, phobic, and obsessive disorders, in *Anxiety: New Research and Changing Concepts*. Edited by Klein DF, Rabkin J. New York, Raven Press, 1981
13. Thoren P, Asberg M, Bertilsson L, et al: Clomipramine treatment of obsessive compulsive disorder, II: biochemical aspects. *Arch Gen Psychiatry* 1980; 37:1289-1294
14. Flament MF, Rapoport JL, Berg CL, et al: Clomipramine treatment of childhood obsessive compulsive disorder, a double blind controlled study. *Arch Gen Psychiatry* 1985; 42:977-986
15. Zohar J, Mueller EA, Insel TR, et al: Serotonergic responsivity in obsessive compulsive disorder. *Arch Gen Psychiatry* 1987; 44:946-951
16. Craven JL, Rodin GM: Cyproheptadine dependence associated with an atypical somatoform disorder. *Can J Psychiatry* 1987; 32:143-145

Experiences of a Paraplegic Psychiatry Resident on an Inpatient Psychiatric Unit

Beryl B. Lawn, M.D.

The author reviews the literature on disabled physicians and describes her own adjustment to paraplegia. While she was a medical student and practicing internist, she encountered few comments about her disability, but during her later psychiatry residency, hospitalized psychiatric patients discussed it frequently. The author presents examples and points out that patients' reactions often revealed much about their characteristic response patterns; reactions to her disability became a type of projective test. Her primary defenses against patients' remarks were intellectualization and isolation of affect. Supervisors who were able to discuss the impact of her disability on the doctor-patient relationship were considered most helpful.

(Am J Psychiatry 1989; 146:771-774)

Although it is estimated that there are between 18,000 and 80,000 physically disabled physicians in practice in the United States (1), the literature contains little about this population and almost nothing about the impact of their disability on their relationships with patients. Two of the best recent review articles on the subject (2, 3) have discussed in depth the demographic characteristics of disabled physicians. Of the 226 disabled physicians and 33 medical students surveyed by Wainapel (3), 133 had neurologic problems (spinal cord injury, multiple sclerosis, and stroke), 48 had musculoskeletal problems (amputation, connective tissue disease, and arthritis), 43 were visually impaired or blind, and 20 had hearing losses. Eighteen percent of the physicians and medical students had become disabled before medical school, and 9% of them had become disabled during medical school or residency. The specialties most highly represented were internal medicine, family practice, psychiatry, rehabilitation medicine, and pediatrics. Only 3% of these disabled physicians had changed specialty because of their disability, and only 18% had retired or

become inactive. In other words, at least three-quarters were in active medical practice.

Semantic confusion continues to exist in the literature about the terms "impaired physician" (i.e., one who abuses alcohol or drugs) and "disabled physician." As has already been pointed out (4), these terms actually refer to two entirely different populations: "impaired" refers to those whose level of function is suboptimal, and "disabled" denotes someone who is cognitively and intellectually intact although physically disadvantaged.

Although the literature pertaining to physical disability and medical practice addresses demographic issues and adaptive equipment and other environmental modifications that facilitate functioning, little has been published about the emotional impact of disability on the physicians themselves or on their patients and colleagues. Some of this material has been addressed in more depth in articles dealing with racial difference, i.e., being a black (5) or Hispanic (6) psychiatric resident in a predominately white medical institution. The problems cited by Jones et al. (5) included absence of black role models, "high praise for what would be considered ordinary achievement by other residents . . . and a reluctance to criticize [the black resident] for shortcomings," and supervisors' tendencies to deal with racial issues by avoidance, reaction-formation, or confrontation. Supervisors who managed to directly address the impact of race on the therapeutic process were viewed as particularly helpful. More typically, however, supervisors "seemed to never notice we were black."

Two other excellent accounts have been written about the impact of illness on physicians and their relationships with colleagues (7, 8). Marzuk (7) dealt exclusively with the "physician-as-patient," while Rabin et al. (8) described more globally the impact on friends and associates of the amyotrophic lateral sclerosis of one of the authors.

Finally, Schwartz (9) wrote a superb article exploring the impact of acute illness in the analyst and its implications for the analytic process. This article was both a description of the author's own illness and its effect on his relationships with patients and a review of the relevant literature. Transference issues (e.g., patients' deepened sense of guilt over their hostile impulses) and countertransference issues (e.g., reparative

Received June 16, 1988; revision received Dec. 7, 1988; accepted Dec. 20, 1988. From the Hahnemann University Hospital, Philadelphia, and the Thomas Jefferson University Hospital, Philadelphia. Address reprint requests to Dr. Lawn, Magee Rehabilitation Hospital, 6 Franklin Plaza, Philadelphia, PA 19102.

Copyright © 1989 American Psychiatric Association.

overidentification or narcissistic nonrelatedness) were explored in depth.

The purpose of this article is to enlarge on the literature already discussed by describing my experiences as a paraplegic resident on an inpatient psychiatric unit and to compare them with my previous experiences as a disabled medical student and practicing internist.

REACTIONS OF PATIENTS

In 1967 I sustained an incomplete T-12 paraplegia as a result of a crime-related injury. Although I had already been accepted into medical school at that time, my injury delayed my starting by 1 year. As a result of intensive rehabilitation and the loving support of my husband, I was totally independent at a wheelchair level and drove my own hand-controlled car when I did begin medical school in 1968. Although immediately after the injury my disability seemed to be the center and focus of my entire life, as the years went by it took an increasingly peripheral role. I often said that in my familiar work and home environment I thought about my wheelchair about as often as I thought about my glasses. Yet I was aware that what was true for me was not generally true for others; *they* were quite aware of the wheelchair and revealed it in their assumptions that I was retarded, unemployed, poor, asexual (my husband was usually labeled my "friend" or "companion" by strangers), and unhappy. During medical school and my later 3-year internal medicine residency, however, it was the unusual patient or patient's family who directly commented on my disability. When they did, it was often to manifest confusion: which cue should they respond to—white coat and stethoscope or wheelchair? Was I a doctor or a patient, a strong and omnipotent parent figure or a dependent and helpless child? Other responses included frequent apologies from patients such as "Why am I complaining about this to you, Doctor, it's so minor compared with your problems," or statements that my success in dealing with my own problems had given them renewed hope in dealing with theirs. I never had the experience most feared by medical students and beginning physicians: rejection by a patient because I was different from most physicians. I attributed this to the ability of a concerned and empathic manner to overcome any initial awkwardness, although it might also have been due to the usual hesitation of patients to question or antagonize their caregivers.

During the first 12 years of my internal medicine practice, my experiences with patients were similar to those I encountered in my training years. Since my disability had played a seemingly small role in my professional life throughout those periods, I was totally unprepared for the response from hospitalized psychiatric patients after I began my psychiatry residency at an inner-city teaching hospital in July 1987.

The first hint of things to come occurred within 15 minutes of my arrival on the inpatient unit: a woman

with a diagnosis of chronic undifferentiated schizophrenia approached me and without further ado inquired pleasantly, "Are you crippled?" It turned out to be *the* question asked by almost every new patient I saw on either inpatient floors or in the psychiatric emergency room. The question was always the same. Their responses to my "Yes, I am" differed markedly, however. Several brief clinical vignettes will highlight the most common responses.

1. A 38-year-old Hispanic woman with a long history of paranoid schizophrenia was brought to the psychiatric emergency room for hostile and assaultive behavior. When initially seen by me, she inquired, "Are you crippled?" and in response to my affirmative response, refused to talk further. When pressed for a reason for her reluctance to speak, she replied, "If I can walk and you can't, how are *you* going to help *me*?"

2. Another woman, who was 32 years old and had also been given a diagnosis of paranoid schizophrenia, had lived on the streets for 5 years, supporting herself by prostitution, and was brought to the emergency room on an involuntary commitment because of poor self-care. When I introduced myself to her, she too inquired, "Are you crippled?" On being told "Yes," she screamed, "You're lying—get out, get out!" then added, "I'll be watching you through the window, and I'll see you when you get up out of that chair and walk. I know what you're up to."

3. A woman with chronic undifferentiated schizophrenia who had strong religious preoccupations approached me daily on the inpatient unit, touching my legs or sprinkling me with "holy" water while quoting from the Bible. She assured me that if my faith was strong enough I would be cured. She was one of a number of patients who told me that they prayed daily for my healing.

4. A 35-year-old man with schizoaffective mania was typical of many of my patients in wanting to push me around the ward in my wheelchair. On some days several patients vied for this privilege, and I was often surprised by who wanted the job—not uncommonly, the most withdrawn or hostile patients on the unit. The manic patients usually won, however.

5. A 32-year-old man with diagnoses of substance abuse and borderline personality disorder became enraged at me one morning and yelled, "I'm not talking to you anymore, you lousy cripple." He was one of several patients who perceived my disability as my area of greatest vulnerability and invoked it when angered.

6. A 22-year-old woman with major depression who did not know me approached me on the psychiatric medical care unit one evening while I was on call and asked if I was particularly tired that evening. When I replied, "No, why?" she said, "Oh, I just thought you were, since you're using the wheelchair."

7. A 23-year-old man with a serious polysubstance abuse problem reminded me of my internal medicine days when he said to me one morning, "It's going to be tough, Doc, but if you can make it with your problems, then so can I."

Several themes run through these brief vignettes. One is the paradox of the disabled physician. For many, "disabled" connotes defective or inferior, whereas being a physician is often equated with power and prestige. A disabled physician becomes an enigma, and the paradox is often most easily resolved by ignoring one or the other attribute. Patient 1 highlighted her assumption that disabled equals defective when she wondered how I could help her if I could not walk. She resolved the disabled physician paradox by assuming that if I actually was a disabled doctor, I must be a second-rate doctor. Perhaps a more seasoned psychiatrist would also argue that she was projecting some of her own feelings of unworthiness onto me. Patient 6 made a different assumption to resolve the paradox; to her, I was using the wheelchair as a convenience because I was tired, and physically I was really normal. Patient 2 believed that I could not really be both disabled and a doctor and concluded that I was feigning disability to fool or disarm her and win her trust. At the opposite end of the spectrum from depreciating or infantilizing the disabled is the tendency of others to idealize successful disabled individuals, making them "super-crips," a tendency seen in mild form in the admiration by patient 7.

In many of these situations, my disability became a lightning rod, both attracting and revealing the patient's characteristic patterns of response. In essence it became a tool, a type of projective test. The other way in which it had a positive effect is highlighted by patient 4. My being hurt or less than perfect lessened the emotional distance patients felt between themselves and me, and even the normally hostile or withdrawn patient felt it was safe to approach, even to care. Perhaps it was one of the few instances in which they could become the caregivers. To what extent this perceived decrease in emotional distance will assist me in long-term outpatient therapeutic relationships remains to be seen. I wonder if the antithesis might not also occur—patients fearing to get close if I am "sick," for fear I may die. This too remains to be seen.

What of my own reactions to my patients' remarks? I have been surprised by my lack of intense emotional response in most situations, especially since I still find pervasive attitudinal barriers the most annoying aspect of my disability. I think prominent among my defenses have been intellectualization and isolation of affect. I conceived the idea of this paper soon after I began training, and I actually welcomed each new relevant incident, however unpleasant, as further grist for the mill. Humor helped, too. I also began using the intensity of my emotional response as a useful diagnostic discriminator; high intensity was often evoked by patients with axis II diagnoses of borderline personality disorder. In the same way that many patients identified with me because I was somehow "defective, too," my own experiences as a patient made me empathize more with their pain and powerlessness. Perhaps, by using displacement and identification, in healing their hurts I was also helping to heal old hurts of my own.

REACTIONS OF SUPERVISORS, TEACHERS, AND OTHER RESIDENTS

Almost without exception, unit directors and supervisors did not discuss my disability unless I raised the issue first, generally in conjunction with discussion of the transference issues cited earlier. Once they were "given permission" to broach the topic, however, their comments were usually insightful and pertinent. As is so often taught to patients undergoing intensive inpatient physical rehabilitation, the onus for making others comfortable with discussing disability is the responsibility of the individual with the disability. I see now that a similar dynamic was operating with my fellow residents. At each of our twice-yearly resident retreats, I chose to lead small group discussions titled "The Experiences of a Disabled Physician." I realize now that the message I was sending was, "See, I can talk about 'it,' and so can you! It's actually a part of who I am!"

The one attending physician who was willing to mention my disability before I did was one of my early and favorite supervisors, who discussed it frankly from the time of my first telephone contact with him while also acknowledging his discomfort in doing so. On one occasion he commented, "I'd be tempted to flush myself down the toilet if that happened to me." On many other occasions he referred to his "oversolicitousness" toward me as a reaction-formation. Despite the ambivalence inherent in these comments, I am still far more comfortable when my disability is addressed directly, rather than when it is ignored. Discussing it, however awkwardly, bespeaks a level of comfort with me in my totality that is absent when it is not mentioned.

Although I am certain that it was harder than usual for either my peers or supervisors to criticize me when it was necessary, I was determined that insofar as possible the need would not arise. Like many overachieving members of minorities before me, I was determined not to fall into any societal stereotypes—in this case, that of the helpless and ineffectual cripple.

COMMENT

As I completed this study of the frequency with which my psychiatric patients focus on my disability, I began to realize that most of my internal medicine patients over the years had probably reacted similarly but had just not talked about it. Perhaps, as Rabin et al. (8) noted, I was behaving as though nothing were unusual, and they simply found it easiest to follow suit. My physical disability was in fact probably only one of my many objective characteristics that resulted in unvoiced transferences in most patients.

I eagerly await my experiences in outpatient psychiatry and hope that other physicians with disabilities will report their experiences as well.

REFERENCES

1. Martini C: Physical disabilities and the study and practice of medicine. *JAMA* 1987; 257:2956-2957
2. Wainapel S: The physically disabled physician. *JAMA* 1987; 257:2935-2938
3. Wainapel S: Physical disability among physicians: an analysis of 259 cases. *Int Disability Studies* 1987; 9:138-140
4. Young M: "Disabled" is not "impaired" (letter). *JAMA* 1987; 258:1173-1174
5. Jones BE, Lightfoot OB, Palmer D, et al: Problems of black psychiatry residents in white training institutes. *Am J Psychiatry* 1970; 127:798-803
6. Oquendo M, Markowitz J: Training and translation: challenges faced by the Hispanic resident. *Hosp Community Psychiatry* 1988; 39:668-669
7. Marzuk P: When the patient is a physician. *N Engl J Med* 1987; 317:1409-1411
8. Rabin D, Rabin PL, Rabin R: Compounding the ordeal of ALS: isolation from my fellow physicians. *N Engl J Med* 1982; 307: 506-509
9. Schwartz H: Illness in the doctor: implications for the psycho-analytic process. *J Am Psychoanal Assoc* 1987; 35:657-692

Patterns of Psychotherapy Utilization

Kenneth I. Howard, Ph.D., Christine V. Davidson, Ph.D.,
Michael T. O'Mahoney, Ph.D., David E. Orlinsky, Ph.D., and Kevin P. Brown, M.S.

Epidemiologic research indicates that a small minority of patients make the great majority of outpatient mental health visits. This small group of long-term patients constitutes the bulk of psychotherapeutic practice and creates a disproportionate impression on mental health professionals. The authors confirmed this finding by studying 405 patients in a clinical setting with an orientation toward long-term psychotherapy: 68% of the patients attended 26 or fewer psychotherapy sessions, representing 23.3% of the total number of sessions used by all patients; 32% attended more than 26 sessions, representing 77% of the total number of sessions used by all patients.

(Am J Psychiatry 1989; 146:775-778)

It has been well documented (1, 2) that the majority of psychotherapy outpatients receive relatively few sessions of treatment. Moreover, there has been much recent emphasis on the provision and evaluation of brief (or time-limited) treatments. Yet, a long-term, typically psychodynamically oriented therapeutic model is still taught in most major training institutions and practiced by the majority of psychotherapists. Studies of the utilization of the psychotherapy service delivery system (3-5) reveal an apparent paradox—the majority of patients attend relatively few sessions, but the majority of therapist time is spent with long-term patients. Long-term patients use the vast majority of services, are usually seen as appropriate for an intensive treatment model, and create an unrepresentative impression on therapists with regard to the general outpatient population. Cohen and Cohen (6) called the notion that the majority of patients are long-term the “clinician’s illusion.”

Epidemiologic surveys provide relevant information about the utilization of outpatient psychotherapy. The National Medical Care Expenditure Survey of 1977-1978 (3) and the National Medical Care Utilization

and Expenditure Survey of 1980 (4) both included assessments of outpatient mental health care utilization. The National Institute of Mental Health (NIMH) Epidemiologic Catchment Area Program (5) specifically addressed the incidence and treatment of mental illness. The results of these surveys are consistent in documenting the fact that although the median length of treatment was quite brief, a small number of patients used the majority of outpatient resources.

In the National Medical Care Expenditure Survey (3), it was reported that 4.6% of the U.S. population made at least one ambulatory mental health visit in a 12-month period. Two percent (3.81 million people) received their mental health care from the “specialty mental health sector” (psychiatrists, psychologists, psychiatric social workers, mental health counselors), making 35.83 million visits. Of people making a mental health visit, 22.2% made only one visit (accounting for about 0.85 million visits), 25.3% made two to four visits (accounting for about 2.89 million visits), and 52.5% made five or more visits (accounting for about 32.09 million visits). This last group (five or more visits) accounted for 89.6% of the visits in a 12-month period. “Most people who use the specialty sector are not high users—almost one half of persons who used this sector had less than five visits. However, the mean number of visits per person . . . was almost ten, thus suggesting that a small proportion of the user population are particularly heavy users” (3, p. 571).

Similarly, in the National Medical Care Utilization and Expenditure Survey (4), the authors reported that 44% of the persons who made a mental health visit to an office-based psychologist or psychiatrist made fewer than four visits and accounted for only 6.7% of the total expenditures. By contrast, 16.2% made more than 24 visits and accounted for 57.4% of the total expenditures.

We have calculated from the original Epidemiologic Catchment Area Program report on utilization (5) that the mean number of sessions for individuals visiting a specialty provider of mental health care was between 10 and 15. Data provided in 1987 by Sam Shapiro (personal communication) have allowed us to evaluate length of treatment for the Greater Baltimore Epidemiologic Catchment Area Program site. At this site, the mean length of treatment was approximately 12 sessions and the median was about four sessions. These estimates are consistent with the national sample esti-

Received March 7, 1988; revision received Nov. 22, 1988; accepted Dec. 20, 1988. From the Institute of Psychiatry, Northwestern Memorial Hospital, Evanston, Ill. Address reprint requests to Dr. Howard, Department of Psychology, Northwestern University, Evanston, IL 60208.

Supported in part by NIMH grant MH-42901.

Copyright © 1989 American Psychiatric Association.

mates and again exhibit the skewed allocation of treatment resources. A relatively small proportion of patients used the bulk of resources.

The national surveys and the Epidemiologic Catchment Area Program focused on utilization during arbitrarily fixed time periods (6 or 12 months). In any arbitrary interval some long-term patients would be just starting therapy and thus would have had only a few sessions at the time they were interviewed. Consequently, the proportion of long-term patients and their use of psychotherapy resources is probably underestimated. To properly assess utilization by long-term patients, we must consider the duration of a treatment episode.

Interest in long-term psychotherapy is justified not only by concern with the health care service provided for a particular segment of the population. A review of process and outcome research (7) found a statistically significant positive association between length of therapy (number of sessions) and treatment outcome in 74 of 114 studies. Only two studies yielded significant negative findings. Of the remaining 38 nonsignificant findings, 36 (95%) showed a positive association between treatment duration and outcome. The results of a subsequent meta-analysis (8) demonstrated a positive linear relationship between dose of psychotherapy and the percent of improvement. Whatever happens later in the course of treatment (whether the onset of a more beneficial stage or simply the steady accumulation of gains) seems to make long-term therapy more effective than service providing a smaller number of sessions.

In the investigation reported in this paper, we analyzed a group of patients entering treatment during a 1-year interval and followed the course of treatment over subsequent years, until the termination of therapy for each patient. After presentation of data on the full sample, we will present comparisons of treatment utilization as a function of the experience level of the therapists.

METHOD

The 405 patients we studied, who entered an outpatient psychotherapy program, were highly selected and were almost all self-referred. To become a patient in this program, one first calls the clinic. A brief telephone interview is conducted by the intake worker, who asks about the nature of the caller's problem and obtains some basic demographic information. If the intake worker decides that the patient is not in crisis and is otherwise suitable for individual psychotherapy, an appointment is made for a screening interview. This interview is conducted by a clinician (typically a psychology or psychiatry resident) and usually takes 1–2 hours. If the clinician also concludes that the patient is suitable for individual psychotherapy, a case summary is sent to the program director, who assigns the patient to a therapist. The therapist then contacts the patient to arrange for the first psychotherapy session.

All patients pay a fee based on their incomes and may also use health insurance to pay for some portion of their care. The average fee is approximately \$50.00 per visit. All patients in our psychotherapy program, regardless of fee or insurance status, are offered open-ended treatment. Patients in our psychotherapy program are very similar to patients seen in many office-based practices.

Two hundred seventy (67%) of the patients in the sample were women, 344 (85%) were 20–39 years old, 336 (83%) were not currently married, 231 (57%) were employed full-time, 57 (14%) were students, 336 (83%) had at least some college education, and 105 (26%) had attended graduate school. In general, the patients were diagnosed as mildly to moderately disturbed.

There were about 80 therapists in our psychotherapy program during the period of this study. Most were psychology or psychiatry residents, but most had had substantial experience. For example, 59 (74%) had already seen at least 20 patients in individual psychotherapy by the time this study was conducted. Forty-eight (60%) of the therapists were psychologists, 23 (29%) were psychiatrists, and nine (11%) were psychiatric social workers; 75 (94%) were between 20 and 39 years old; 43 (54%) were men; 43 (54%) were married; and 66 (83%) had had personal therapy.

The guiding orientation of our psychotherapy program is psychodynamic, or psychoanalytic in the broad sense. All of the supervisors espouse this therapeutic approach (unpublished 1988 paper by C. McNeilly and K.I. Howard), and case presentations follow this model. Attempts are made to conceptualize the case of each patient from a psychodynamic perspective. For example, the medical record requires that every therapist complete a dynamic formulation of each patient after the sixth therapy session. Needless to say, treatment is not guided by an explicit manual and treatment integrity is checked only by means of case supervision. It is our impression that the therapy conducted in this program is broadly representative of the psychotherapeutic services generally delivered in the United States.

RESULTS

Table 1 shows that the largest single percentage (24%) of the 405 patients who began treatment attended fewer than five sessions of psychotherapy. Thirty-two percent of the patients stayed in treatment for more than 26 sessions (6 months of once-a-week sessions). The median length of treatment for the 405 patients was about 13 sessions (mean=26.5; range=1–207); the median treatment duration for patients who completed four sessions, however, was 21 sessions, and the median for patients who completed eight sessions was 28 sessions. These figures illustrate the importance of the initial phase of therapy in deter-

TABLE 1. Relationship of Number of Sessions to Type of Medical Plan and Experience of Therapists for 405 Patients in a Psychotherapy Clinic

Length of Treatment	Patients											
	Sessions (N=10,749)		HMO Participant (N=53)		Non-HMO Participant (N=352)		Had Staff Therapist (N=65)		Had Trainee Therapist (N=340)		Total (N=405)	
	N	%	N	%	N	%	N	%	N	%	N	%
1-4 sessions	236	2.2	12	22.6	85	24.2	12	18.5	85	25.0	97	24.0
5-8 sessions	426	4.0	12	22.6	54	15.3	11	16.9	55	16.2	66	16.3
9-16 sessions	686	6.4	3	5.7	53	15.1	10	15.4	46	13.5	56	13.8
17-26 sessions	1,152	10.7	13	24.5	42	11.9	3	4.6	47	13.8	55	13.6
27-52 sessions	2,215	20.6	8	15.1	57	16.2	10	15.4	55	16.2	65	16.0
53-78 sessions	1,721	16.0	3	5.7	25	7.1	2	3.1	26	7.6	28	6.9
79-104 sessions	2,003	18.6	1	1.9	21	6.0	3	4.6	14	4.1	22	5.4
>104 sessions	2,310	21.5	1	1.9	15	4.3	4	6.2	12	3.5	16	4.0

mining treatment duration and (by implication) outcome as well.

Table 1 also shows that the patients who attended one to four sessions accounted for only 2% of the total number of sessions attended by all 405 patients. The 131 (32%) patients who attended more than 26 sessions accounted for 77% of the sessions used. The 66 (16%) patients who stayed in therapy for more than 52 sessions used more than 56% of the sessions.

Fifty-three of the patients were participants in a health maintenance organization (HMO). These patients were entitled to 20 sessions of psychotherapy in any 12-month period. Table 1 shows the number of sessions these patients attended compared with the rest of the patients. Twelve (23%) of the HMO patients attended fewer than five sessions, and 13 (25%) attended more than 26. The median length of treatment of the 53 HMO participants was about 14 sessions (mean=21.5; range=1-153). The median duration of treatment for the HMO participants who completed four sessions was 19 sessions, and the median duration for those who completed eight sessions was 24 sessions. For five (10%) of the 53 HMO participants, their 20th psychotherapy session was their last. Eighteen (34%), however, continued treatment beyond the 20-session limit, compared with 137 (39%) of the rest of the patients (data not shown).

HMO patients who completed eight sessions of treatment had a probability of 0.90 of continuing beyond 16 sessions (26 [90%] of the 29 HMO patients who completed eight sessions also completed 16 sessions); for the non-HMO participants, this probability was 0.75 (160 [75%] of the 213 non-HMO patients who completed eight sessions also completed 16 sessions). The patients who were HMO participants were significantly different from the patients who were not in that fewer HMO participants tended to terminate treatment in the 9-16-session range and more tended to terminate treatment in the 17-26-session range ($\chi^2=11.66$, $df=5$, $p<0.05$). The overall pattern of utilization of the HMO participants, however, was similar to that of the rest of the patients. (To ensure ade-

quate cell sizes for the chi-square analyses, we used six length-of-treatment groups rather than the eight shown in table 1. The six were 1-4, 5-8, 9-16, 17-26, 27-52, and more than 52 sessions.)

Sixty-five of the 405 patients were seen by staff therapists and 340 were seen by therapists who were at various stages in their training. Table 1 shows the treatment duration of these groups of patients. There was a nonsignificant trend toward a difference between these groups in length of treatment ($\chi^2=2.54$, $df=5$, $p>0.05$). The median length of treatment was about 15 sessions for the patients whose therapist was a staff member (mean=33.0; range=1-153); it was 13 sessions (mean=25.3; range=1-207) for patients whose therapist was a trainee. A greater percentage of the sessions of patients with trainee therapists were allocated to the initial phase of treatment (sessions 1-4). The two-session discrepancy in medians is thus mostly attributable to differences in retention of patients beyond the initial sessions: 53 (82%) of the patients seen by a staff therapist continued beyond the fourth session, compared with 255 (75%) of the patients seen by trainees. Ancillary analyses ruled out the possibility that the difference in length of therapy among the patients with trainee therapists was an artifact of the length of the trainees' rotation in the clinic.

Despite the nonsignificant trend for patients of trainees to terminate therapy earlier, 31% of their patients completed more than 26 sessions of psychotherapy, compared with 37% of the patients of staff therapists. The patients who completed more than 26 sessions accounted for 76% of the treatment sessions provided by trainee therapists and 81% of the sessions provided by the staff therapists (data not shown).

DISCUSSION

The results of this study support Cohen and Cohen's concept of the "clinician's illusion" that the typical patient is in long-term therapy (6). In fact, a minority of the patients in our program used the vast majority

of resources. Long-term patients dominate a clinician's practice and thus his or her time, even though most patients do not engage in long-term psychotherapy. Since so few of the sessions conducted by therapists are in the initial phase of treatment, therapists may not be sufficiently aware of the critical role of this phase in shaping the patient's treatment.

National surveys have attempted to relate a number of patient variables to psychotherapy utilization. The effect of insurance coverage has been of particular interest, given the orientation toward national health policy planning of the investigators. Horgan (3), analyzing the National Medical Care Expenditure Survey data, found that the number of visits was negatively related to the percentage of the cost paid out of pocket. Taube et al. (4), analyzing the National Medical Care Utilization and Expenditure Survey data, found that the demand for mental health services was responsive to price, but not for patients with yearly incomes greater than \$25,000. In contrast to these findings, Keeler et al. (9), reporting on the Rand Health Insurance Experiment, found that although coinsurance appeared to influence the decision to use mental health services negatively, coinsurance was not related to level of use when there was any use. Watts et al. (10), analyzing utilization in a study of the Federal Employees Health Benefits Program, found that level of use in a heavily insured population within a year was not responsive to price, but they also observed that the range of variation in out-of-pocket expenses was rather small in that study.

We have not presented data here that are relevant to whether insurance coverage affects the likelihood that a person will call for an appointment. However, insurance coverage (as estimated from our group of HMO participants) seemed to have only a limited impact on the amount of utilization of psychotherapy once the patient entered treatment. The median lengths of treatment for HMO participants and nonparticipants were almost identical. The only effect of insurance coverage seemed to be that it increased utilization during one phase of treatment.

With regard to the comparison of staff and trainee therapists, there was a trend for patients of trainees to terminate therapy earlier than those of staff therapists. The mean length of treatment for patients of staff therapists was about eight sessions greater than that of trainees, and this seemed to be mostly due to the greater proportion of trainees' patients who terminated therapy in the first four sessions.

The estimated median duration of psychotherapy in the United States is five to eight sessions (1, 2). About

16% of patients use more than 24 sessions in a 12-month period (4). The median length of treatment in our psychotherapy program was almost twice as long (13 sessions), and 32% of the patients went beyond 26 sessions. To some extent, this was due to the fact that we included the entire course of treatment for the patients studied rather than 12-month utilization rates. Studies that concentrate on use during a 12-month period would miss data on patients whose treatment lasted for more than 12 months as well as on long-term patients who did not enter psychotherapy until the end of the year surveyed. Our higher median was also probably due to the careful selection procedures used in our program and the fact that the patients had a pretherapy screening interview. In any case, 13 sessions of treatment do not qualify as long-term psychotherapy, and half of the patients in our program had terminated by the 13th session.

Despite the program's emphasis on long-term psychodynamic psychotherapy, the vast majority of patients were exposed to a brief therapy and the vast majority of professional resources were concentrated on the relatively few patients who engaged in long-term treatment.

REFERENCES

1. Garfield SL: Research on client variables in psychotherapy, in *Handbook of Psychotherapy and Behavior Change*, 3rd ed. Edited by Garfield SL, Bergin AE. New York, John Wiley & Sons, 1986
2. Phillips EL: *Psychotherapy Revised: New Frontiers in Research and Practice*. Hillsdale, NJ, Lawrence Erlbaum Associates, 1985
3. Horgan CM: Specialty and general ambulatory mental health services. *Arch Gen Psychiatry* 1985; 42:565-572
4. Taube CA, Kessler L, Feuerberg M: Utilization and expenditures for ambulatory mental health care during 1980, in *National Medical Care Utilization and Expenditure Survey: Data Report 5*. Washington, DC, DHHS, 1984
5. Shapiro S, Skinner EA, Kessler LG, et al: Utilization of health and mental health services: three Epidemiologic Catchment Area sites. *Arch Gen Psychiatry* 1984; 41:971-978
6. Cohen P, Cohen J: The clinician's illusion. *Arch Gen Psychiatry* 1984; 41:1178-1182
7. Orlinsky DE, Howard KI: Process and outcome in psychotherapy, in *Handbook of Psychotherapy and Behavior Change*, 3rd ed. Edited by Garfield SL, Bergin AE. New York, John Wiley & Sons, 1986
8. Howard KI, Kopta SM, Krause MS, et al: The dose-effect relationship in psychotherapy. *Am Psychol* 1986; 41:159-164
9. Keeler EB, Wells KB, Manning WG, et al: *The Demand for Episodes of Mental Health: R-3432-NIMH*. Santa Monica, Calif, Rand Corp, 1986
10. Watts CA, Scheffler RM, Jewell NP: Demand for outpatient mental health services in a heavily insured population: the case of Blue Cross and Blue Shield Association's Federal Employees Health Benefits Program. *Health Services Research* 1986; 21: 267-289

Hypersensitivity to Carbon Dioxide in Panic Disorder

Laszlo A. Papp, M.D., Raymond Goetz, Ph.D.,
Randolph Cole, M.D., Donald F. Klein, M.D., Fancha Jordan,
Michael R. Liebowitz, M.D., Abby J. Fyer, M.D.,
Eric Hollander, M.D., and Jack M. Gorman, M.D.

Seven male panic patients did not panic but were significantly more sensitive to steady-state carbon dioxide inhalation than five male normal control subjects. The male patients' hypersensitivity to carbon dioxide was unrelated to current state of anxiety or acute panic.

(Am J Psychiatry 1989; 146:779-781)

It has been established that carbon dioxide (CO₂) inhalation induces panic in panic disorder patients with or without agoraphobia (1-3). During CO₂ challenge the point of panic seems to coincide with the highest blood CO₂ concentration (3). CO₂-induced panic attacks are phenomenologically similar to lactate-induced attacks and involve similar biochemical and physiological changes (1).

One possible explanation for CO₂-induced panic is that panic patients are biologically hypersensitive to CO₂ (1). Two commonly used methods of determining CO₂ sensitivity are the steady-state canopy procedure (4) and the rebreathing method (5). With both, minute volume (respiratory frequency × tidal volume) is measured at different concentrations of inhaled CO₂, and the ratio of change in minute volume to change in

expired or arterial PCO₂ is called ventilatory response or CO₂ sensitivity.

The literature on ventilatory response in panic disorder patients is inconclusive. In two of three studies (1, 2, and unpublished study by D. Carr et al.), CO₂ sensitivity in panic patients was greater than in control subjects.

These studies, however, were confounded by inherent technical and design problems. The mouthpiece-noseclip arrangement in the rebreathing method, as opposed to the canopy in the steady-state procedure (4), could itself induce anxiety. The high baseline CO₂ concentration used in the rebreathing bag may mask subtle differences between patients and control subjects. Finally, to our knowledge, none of the studies evaluated the CO₂ sensitivity of nonpanicking panic patients separately; therefore, data are not available regarding differences in CO₂ sensitivity between patients and control subjects unrelated to CO₂-induced anxiety.

The present analysis was part of a complex study of respiratory physiology in panic disorder that was designed to compare the anxiogenic effects of CO₂ inhalation and hyperventilation. Our goal was to determine CO₂ sensitivity with the steady-state canopy method in patients who did not panic during CO₂ challenge, achieved steady-state minute volume, and therefore demonstrated ventilatory changes independent of the state of their anxiety.

METHOD

The subjects described here participated in a previously reported study that involved the administration of 5% CO₂ in a canopy (1). Since CO₂ sensitivity determination requires arterial blood samples, data were

Received June 2, 1988; revision received Oct. 20, 1988; accepted Dec. 1, 1988. From the Biological Studies Unit, New York State Psychiatric Institute, and the Department of Psychiatry and Medicine, College of Physicians and Surgeons, Columbia University, New York. Address reprint requests to Dr. Papp, New York State Psychiatric Institute, 722 West 168th St., New York, NY 10032.

Supported in part by grant MH-33422, grant MH-30906, Physician Training in Clinical and Treatment Research grant MH-15144 (Dr. Papp), and Research Scientist Development Award MH-00416 (Dr. Gorman) from NIMH.

Copyright © 1989 American Psychiatric Association.

available for only 11 patients (seven men and four women) who had *DSM-III* panic disorder or agoraphobia with panic attacks and nine normal control subjects (five men and four women) who did not panic during CO₂ challenge. There were no significant age differences between the groups. All subjects had been drug free for at least 4 weeks and had fasted for 8 hours before the procedure. Intermittent use of a short-acting benzodiazepine (1 mg of alprazolam or equivalent) was permitted up to 3 days before the study. Written informed consent was obtained.

The subjects were told that CO₂ would be added to the air they were breathing and that they might experience anxiety. Under local anesthesia an arterial catheter was inserted in the radial artery of the supine subject for blood withdrawal. Then the subject's head was placed in a clear plastic canopy that was vented with fresh air at 40 liters/min. The subject could see and be seen and hear and be heard at all times while in the canopy. Minute volume was measured throughout the procedure on a breath-by-breath basis (4).

The protocol, described in detail elsewhere (1), started with the patient spontaneously breathing room air in the canopy for 20 minutes, then inhaling 5% CO₂ in room air for 20 minutes. The attending psychiatrist was not blind to diagnosis and knew when the CO₂ was given. The patient was instructed throughout to report any physical or emotional symptoms as soon as they occurred. Otherwise, conversation between the subject and staff during the experiment was not permitted.

Arterial blood samples for blood gases were drawn immediately before and immediately after the subject received the CO₂. Ratings on the Acute Panic Inventory and blood pressure were also determined before and after CO₂ inhalation. The Acute Panic Inventory is a 17-item checklist rating the degree of anxiety on a scale of 0 (none) to 3 (severe).

Data Analysis

Steady-state minute volume was achieved in all subjects after 10 minutes of CO₂ inhalation (less than 5% variation over timed 1-minute intervals). The last 2 minutes of the baseline and of the 5% CO₂ period were used to calculate an average minute volume. With the corresponding arterial PCO₂ values, a slope was determined ($\Delta V_E / \Delta PaCO_2$). We then compared the slopes of the two groups (nonpanicking patients and control subjects). Because of the high degree of variance, nonparametric Mann-Whitney U tests were used in this comparison. Analysis of variance with repeated measures (ANOVAR) was used to test for differences in anxiety between the patients and control subjects.

RESULTS

There were no significant slope differences (\pm SD) between the patients and control subjects (5.47 ± 5.82

versus 3.50 ± 3.98 liters/min per mm Hg). The earlier reported sex differences in panic disorder patients (6, 7) prompted an analysis of the male sample separately. The nonpanicking male panic patients were significantly more sensitive to CO₂ than the male control subjects (8.07 ± 5.87 versus 2.49 ± 2.14 liters/min per mm Hg; $z=2.03$, $df=10$, $p<0.043$, two-tailed). Inspection of the individual slopes showed that six of the seven male patients but only one of the five control subjects had slope values above 2.5 liters/min per mm Hg.

Changes in anxiety levels, as measured by the Acute Panic Inventory, were small and did not significantly differ between the male patients and control subjects. The baseline values (mean \pm SD) increased from 2.6 ± 3.9 to 4.0 ± 3.9 in the patients and from 0.9 ± 1.1 to 3.7 ± 3.4 in the control subjects. No significant correlations were found between the slopes and the changes in anxiety levels within the two groups. Unfortunately, there were not enough female subjects for meaningful statistical comparison.

DISCUSSION

Male panic disorder patients were significantly more sensitive to steady-state CO₂ inhalation than male control subjects. The greater CO₂ sensitivity was not associated with a higher anxiety level in this patient group. These preliminary findings represent one of the few biological differences between panic disorder patients and control subjects that is not directly related to current state of anxiety or to acute panic.

The limitations of our study are the small sample size and the absence of an analyzable female sample. Although statistically not meaningful, our data suggest that female panic patients may not be hypersensitive to CO₂. If true, this finding would be consistent with earlier reports of sex differences in panic disorder (6, 7).

We did not control for a number of psychological factors (e.g., cognitive set, personality) known to affect CO₂ sensitivity (8). Cognitive manipulations appear to alter the quality of anxiety in response to panic-inducing procedures (9). In fact, many investigators believe that CO₂-induced panic is the result of misinterpreted uncontrollable physiologic changes (10). In this sample that we studied, however, all subjects received identical instructions and experienced the same degree of anxiety. Thus, reference to cognitive set alone cannot explain the patient/control differences in CO₂ sensitivity. At the same time, CO₂ sensitivity differences alone are insufficient to explain the similar behavioral response to CO₂ challenge in patients and control subjects.

REFERENCES

1. Gorman JM, Fyer MR, Goetz R, et al: Ventilatory physiology of patients with panic disorder. *Arch Gen Psychiatry* 1988; 45:31-39
2. Woods SW, Charney DS, Loke J, et al: Carbon dioxide sensitivity in panic anxiety: ventilatory and anxiogenic response to

- carbon dioxide in healthy subjects and patients with panic anxiety before and after alprazolam treatment. *Arch Gen Psychiatry* 1986; 43:900-909
3. Griez E, van den Hout MA, Verstaappen F: Body fluids after CO₂ inhalation: insight into panic mechanisms? *Eur Arch Psychiatry Neurol Sci* 1987; 236:369-371
 4. Kinney JM, Morgan AP, Domingues FJ: A method for continuous measurement of gas exchange and expired radioactivity in acutely ill patients. *Metabolism* 1964; 13:205-211
 5. Read DJ: A clinical method for assessing the ventilatory response to carbon dioxide. *Aust Ann Med* 1967; 16:20-32
 6. Papp LA, Gorman JM: Sex differences in panic disorder (letter). *Am J Psychiatry* 1988; 145:766
 7. Papp LA, Martinez J, Gorman JM: Arterial epinephrine levels in panic disorder. *Psychiatr Res* 1988; 25:111-112
 8. Saunders NA, Heilpern S, Rebuck AS: Relation between personality and ventilatory response to carbon dioxide in normal subjects: a role in asthma? *Br Med J* 1972; 1:719-721
 9. Rapee R, Mattick R, Murrell E: Cognitive mediation in the affective component of spontaneous panic attacks. *J Behav Ther Exp Psychiatry* 1986; 17:245-253
 10. Margraf J, Ehlers A, Roth WT: Sodium lactate infusions and panic attacks: review and critique. *Psychosom Med* 1986; 48:23-51

ECT for Major Depression in Four Patients Infected With Human Immunodeficiency Virus

Frederick W. Schaerf, M.D., Ph.D., Robyn R. Miller, B.S.,
John R. Lipsey, M.D., and Robert W. McPherson, M.D.

The authors describe four individuals infected with the human immunodeficiency virus type I (HIV) whose severe depressions were successfully treated with ECT. (Am J Psychiatry 1989; 146:782-784)

There have been many case reports and studies describing neuropsychiatric manifestations of acquired immune deficiency syndrome (AIDS) (1-7), but there have been few documentations of specific interventions for the treatment of such disorders (2, 6, 8, 9). Although major depression is not the most frequent psychiatric manifestation of infection with human immunodeficiency virus type I (HIV), it does occur in many patients (3, 5, 6). Delusional depression has also been described in such individuals (4).

The effectiveness of ECT for individuals with severe depression, especially those who do not respond to medications or who have delusions, is well established (10). To our knowledge, however, there are no reports in the literature on the use of ECT in HIV-infected individuals who suffer from major depression. We report here the successful treatment with ECT of four patients with major depression, three of whom were HIV-seropositive and one of whom had AIDS.

CASE REPORTS

Case 1. A 35-year-old gay white man with AIDS was transferred to our psychiatric ward after attempting suicide. He had tried to hang himself with pajamas while receiving inpatient psychiatric treatment at another hospital. The patient had had a successfully treated episode of *Pneumocystis carinii* pneumonia 4 months before this admission. Despite previous treatment with doxepin and alprazolam, he complained of dysphoria, fatigue, hypersomnolence, decreased

energy, and anhedonia. He believed that he was a bad person and had persistent suicidal ideation. Results of physical examination, including complete neurological assessment with neuropsychological testing, were essentially normal except for striking psychomotor retardation. The patient received 12 ECT treatments, after which all of his depressive symptoms resolved.

Case 2. A 35-year-old gay white man infected with HIV was diagnosed as having major depression with psychotic features after coming to the outpatient AIDS clinic with complaints of low mood, anhedonia, decreased sleep and appetite, and intermittent suicidal ideation. Despite knowing the medical evidence to the contrary, he had the delusion that he had a fungal infection of the brain and was going to die of dementia. He was admitted to our hospital, and pharmacotherapy with nortriptyline was initiated, but on the third hospital day he began to experience auditory hallucinations and paranoid delusions and then slashed his neck and wrist in a suicide attempt. ECT was started, and the patient's dysphoria, vegetative symptoms, and psychotic symptoms resolved.

Case 3. A 27-year-old bisexual white man was diagnosed as having major depression 1 month after learning that he was HIV seropositive. He complained of dysphoria, anxiety, and guilt over his bisexual relationships. He had the delusion that he was dying of heart disease. At this time he was admitted to our hospital and treated with amitriptyline, alprazolam, and haloperidol for 25 days. Three days after discharge he came back to the hospital, stating that he felt that he was being punished by the devil. He reported hearing a man's voice telling him to cut his throat. ECT was initiated, and his depression and psychotic features slowly cleared.

Case 4. A 34-year-old single black woman became severely depressed after learning that she was HIV seropositive. She was subsequently hospitalized twice for major depression and treated with doxepin and chlorpromazine without much improvement in symptoms. She came to our hospital with a profoundly depressed mood, guilt, hopelessness, and multiple somatic delusions. She felt that her body was decomposing and being regurgitated into her mouth. She believed that the ECG machine had caused a circle to form around her heart and navel and was preventing her from eating. Her depressive symptoms and delusions quickly resolved with ECT.

Received Aug. 9, 1988; revision received Dec. 7, 1988; accepted Dec. 20, 1988. From the Department of Psychiatry and Behavioral Sciences and the Department of Anesthesia and Critical Care Medicine, Johns Hopkins Hospital. Address reprint requests to Dr. Schaerf, Johns Hopkins Hospital, Osler 320, 600 North Wolfe St., Baltimore, MD 21205.

Copyright © 1989 American Psychiatric Association.

TABLE 1. Summary of Case Reports of Four Patients With AIDS or HIV Infection and Major Depression Treated With ECT

Item	Case 1	Case 2	Case 3	Case 4
Sex	Male	Male	Male	Female
Diagnosis	AIDS	HIV infection	HIV infection	HIV infection
Risk group	Homosexual	Homosexual	Bisexual	Former intravenous drug user
Time from AIDS or HIV diagnosis to onset of depressive symptoms	4 months	2 months	1 month	10 months
Family history of depression	Positive	Negative	Positive	Negative
Personal history of depression	Positive	Negative	Positive	Negative
Results of neurological examination	Within normal limits	Within normal limits	Within normal limits	Within normal limits
Results of lumbar puncture	Raised protein level	Within normal limits	Within normal limits	Within normal limits
Results of CT or MRI	MRI showed diffuse cortical atrophy	CT within normal limits	CT within normal limits	CT within normal limits
Mini-Mental State score	28	30	29	30
Number of right unilateral ECTs	12	10	6	6
Psychotropic drug used for maintenance therapy	Desipramine	Lithium	Lithium and amitriptyline	Nortriptyline
Response to treatment for depression	No relapse (patient died 4 months after discharge)	No relapse at 21-month follow-up	No relapse at 22-month follow-up	No relapse at 20-month follow-up

DISCUSSION

To our knowledge, this is the first report of the successful treatment with ECT of major depression in HIV-infected patients. According to the data shown in table 1, the mean time from known seropositivity or diagnosis of AIDS to onset of depression was 4.3 months. Two patients had neither a personal nor a family history of depressive disorder that might predispose them to the development of a depressive episode, and two patients had had previous episodes of depression and positive family histories (table 1). None of the patients suffered any untoward effects following ECT. Six to twelve treatments were effective in all these patients (table 1); this is the usual range of number of treatments in a course of therapy for noninfected individuals (10).

The effectiveness of the ECT was measured by using Montgomery-Asburg Depression Rating Scale scores. These fell from a mean of 36 before treatment to a mean of 4 following treatment. Mini-Mental Status Examination scores for all patients remained between 28 and 30 (out of a possible 30) throughout treatment. Three of the patients have received maintenance therapy with lithium, a tricyclic antidepressant, or a combination of the two without psychiatric relapse. The fourth patient had no relapse while receiving desipramine before his death from AIDS (table 1).

A previous report of AIDS patients suffering from depression with delusional features (7) implicated organic brain syndrome as the cause. Unlike that report, in which the patients had associated cognitive deficits, all of the patients described here were in clear con-

sciousness, had no history of a cognitive decline, and had no cognitive deficits noted during or after right unilateral ECT.

Our patient with AIDS showed nonspecific mild abnormalities on his pre-ECT magnetic resonance imaging (MRI) study and lumbar puncture studies. Neuropsychological testing performed on this patient, however, did not reveal any evidence of cognitive impairment. Furthermore, the other three patients displayed no evidence of cognitive decline on neuropsychological testing.

The acute onset of a severe depressive syndrome in an individual who is HIV seropositive or who has AIDS warrants initial exclusion of other CNS pathology by means of a full neurological examination, lumbar puncture, and imaging studies such as CT scan or MRI. Despite the fact that HIV has known neurotropic properties (1), its role in the development of depression is not clear. Although the nonspecific finding of slightly elevated CSF protein and the mild atrophy noted on the MRI scan of our patient with AIDS might suggest cerebral HIV infection, there was no clear evidence that CNS infection with HIV had occurred in any of our patients. Further studies, including detection and culture of HIV in CSF, may help answer this question in other patients.

Severe depression in nondemented patients with HIV infection or AIDS appears to respond as well to ECT as does depression in individuals not infected with HIV. As in noninfected patients, the decision regarding ECT is based on the clinical severity of the depressive episode, the failure of pharmacological treatment, and the absence of contraindications.

Therefore, ECT should be considered as a therapeutic option in cognitively intact patients with HIV infection who are suicidal, deluded, or have not responded to other treatments, once other CNS pathology has been excluded. ECT for such patients who are severely depressed and demented warrants further study.

REFERENCES

1. McArthur JC: Neurologic manifestations of AIDS. *Medicine* 1987; 66:407-437
2. Ostrow D, Grant I, Atkinson H: Assessment and management of the AIDS patient with neuropsychiatric disturbances. *J Clin Psychiatry* 1988; 49(May Suppl):14-22
3. Perry SW, Tross S: Psychiatric problems of AIDS inpatients at the New York Hospital: preliminary report. *Public Health Rep* 1984; 99:200-205
4. Perry S, Jacobsen P: Neuropsychiatric manifestations of AIDS-spectrum disorders. *Hosp Community Psychiatry* 1986; 37: 1001-1005
5. Dilley JW, Ochitill HN, Perl M, et al: Findings in psychiatric consultations with patients with acquired immune deficiency syndrome. *Am J Psychiatry* 1985; 142:82-86
6. Frierson RL, Lippman SB: Psychological implications of AIDS. *Am Fam Physician* 1987; 35:109-116
7. Kermani E, Drob S, Alpert M: Organic brain syndrome in three cases of acquired immune deficiency syndrome. *Compr Psychiatry* 1984; 25:294-297
8. Ayd FJ: Psychopharmacotherapy for HIV-infected, AIDS-related complex (ARC), and AIDS patients. *Int Drug Therapy Newsletter* 1988; 23:25-28
9. Abrams DI: Routine care and psychosocial support of the patient with acquired immunodeficiency syndrome. *Med Clin North Am* 1986; 70:707-721
10. Electroconvulsive therapy: Consensus development conference statement. *Natl Inst Health Consensus Dev Conf Consensus Statement* 1985; 5(11):8

Age at Onset in Late-Life Delusional Depression

J. Craig Nelson, M.D., Yeates Conwell, M.D., Kathy Kim, M.D.,
and Carolyn Mazure, Ph.D.

Mean age at onset was not significantly different in 39 delusional and 70 nondelusional unipolar depressed patients over 60 years of age. The finding was unchanged when sex, concurrent dementia, and medical illness were examined.

(Am J Psychiatry 1989; 146:785-786)

Meyers and associates have reported that late-life depression is more commonly delusional (1) and that elderly patients with unipolar delusional depression have a later age at onset than their nondelusional counterparts (2). Their findings had important implications, since they suggested that late-onset depression may be a specific subtype, that age at onset may influence the presentation of depression, and that depressions occurring in later life may be associated with degenerative changes in the brain, resulting in greater cognitive disturbance.

Previous studies have not noted an older onset in delusional patients (3-6). The largest study (7) compared 145 psychotic with 119 nonpsychotic depressed patients and found no difference in the age at onset. Meyers and Greenberg (2) suggested that a later onset in elderly delusional patients may have been missed because these studies included few elderly patients. To explore this question, we examined age at onset in 109 depressed patients over the age of 60 who were admitted to a psychiatric unit in a general hospital.

METHOD

This study is part of a larger investigation of 168 patients over the age of 60 years who were consecutively admitted to the Adult Psychiatric Treatment Unit at Yale-New Haven Hospital during the period 1979 to 1984 (8). The current study included only

patients with a primary diagnosis of unipolar major depression. Diagnoses were made according to *DSM-III* criteria by one of the authors (J.C.N.), who was the attending psychiatrist for all of the patients, using information available from the patient, family, and referring clinician. Patients were excluded if 1) they did not have major depression, 2) their depression was thought to be caused by a specific illness or medication, i.e., organic affective syndrome (five cases), or 3) their primary diagnosis was dementia with depressive features. Patients with concurrent medical illness that was not etiologically related to the depression were included. Also included were 13 patients who had a mild dementia that appeared to be independent of the depression. The diagnosis of depressive delusions followed the definition of the Schedule for Affective Disorders and Schizophrenia (9) and was consistent with our prior studies (3, 4).

Ratings of age at onset, number of prior episodes, number of prior hospitalizations, and duration of the current episode were made from information in the medical record by nurse raters who were blind to diagnosis. Data were available for all four items in 107 of the 109 patients included. Duplicate ratings of these items in 25 cases indicated adequate interrater reliability (intraclass correlation coefficients of 0.95 to 0.99, $p < 0.001$).

RESULTS

Of the 168 patients reviewed, 59 were excluded; 20 patients were not depressed, and 39 had another type of affective disorder. Of the 109 patients with *DSM-III* unipolar major depression, 39 were delusional and 70 were nondelusional. Twenty-seven (69%) of the 39 delusional and 54 (77%) of the 70 delusional patients were women ($\chi^2 = 0.46$, $df = 1$, $p = 0.50$). The delusional and nondelusional groups did not differ with regard to mean \pm SD index age (68.5 ± 6.3 versus 69.9 ± 6.8 years; $t = 1.03$, $df = 107$, $p = 0.30$) or mean number of prior episodes (2.4 ± 2.5 versus 2.3 ± 2.3 ; $t = 0.23$, $df = 106$, $p = 0.82$). The percentages of patients with no prior episode were almost identical (25.6% versus 27.1%). Delusional patients had more prior hospitalizations (1.9 ± 2.1 versus 1.1 ± 1.5 ; $t = 2.01$, $df = 106$, $p = 0.028$). Mean \pm SD duration of the episode was 7.8 ± 7.7 months for the delusional patients and

Received Sept. 28, 1988; revision received Dec. 13, 1988; accepted Dec. 20, 1988. From the Department of Psychiatry, Yale University School of Medicine, and the University of Rochester School of Medicine and Dentistry, Rochester, N.Y. Address reprint requests to Dr. Nelson, Department of Psychiatry, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06510.

Supported in part by NIMH grants MH-30020 and MH-40381 and by a grant from Merrell Dow Pharmaceuticals.

Copyright © 1989 American Psychiatric Association.



11.0 \pm 7.7 months for the nondelusional patients ($t=1.4$, $df=105$, $p=0.16$).

The mean age at onset in the two groups was not significantly different; for the delusional patients it was 51.1 \pm 15.7 years, and for the nondelusional patients it was 55.2 \pm 14.5 years ($t=1.3$, $df=105$, $p=0.17$). In the group with recurrent depression, the delusional and nondelusional patients had mean ages at onset of 45.8 \pm 14.8 and 50.4 \pm 13.5 years, respectively ($t=1.4$, $df=76$, $p=0.17$). The median age at onset for the cohort was 57. Twenty-one (37%) of the 57 patients whose onset was on or before age 57 were psychotic, while 17 (34%) of the 50 whose onset was after age 57 were psychotic ($\chi^2=0.01$, $df=1$, $p=0.92$).

Because of the possibility that a later onset occurs primarily in women with delusional depression (2), age at onset was examined in the 81 female patients. Delusional women had a slightly younger age at onset than nondelusional women (49.8 \pm 15.4 versus 55.2 \pm 14.1 years), but this difference was not significant ($t=1.55$, $df=77$, $p=0.13$).

Thirteen of the 109 patients had a secondary diagnosis of dementia. When these patients were excluded, the index age of the delusional patients was slightly younger (mean \pm SD age=67.3 \pm 5.2 versus 70.0 \pm 6.8 years; $t=2.07$, $df=92$, $p=0.04$); however, their mean age at onset was not significantly different from that of the nondelusional patients (51.9 \pm 15.9 versus 54.7 \pm 14.6 years; $t=0.86$, $df=92$, $p=0.39$).

Ninety percent of the elderly patients had concurrent medical illness. In 29 of the 98 medically ill patients, the illness was currently symptomatic. The proportion of these cases was similar in the delusional and nondelusional groups (eight of 39 versus 21 of 70 patients; $\chi^2=0.72$, $df=1$, $p=0.39$). When patients with active medical illness were excluded, age at onset became significantly younger in the delusional patients than in the nondelusional patients (49.8 \pm 16.6 versus 57.5 \pm 13.4 years; $t=2.28$, $df=77$, $p=0.026$). When sex, dementia, and medical illness were simultaneously entered in a regression with age at onset and delusional status, the relationship between age at onset and delusional status was unchanged.

DISCUSSION

Our elderly sample of patients with unipolar major depression appears similar to that described by Meyers and Greenberg, but our delusional patients did not have a later age at onset. In the Meyers and Greenberg sample, patients were admitted to one of three geriatric units in a private psychiatric hospital; in our study, private patients were admitted to a psychiatric unit in

a general hospital. Although admitting practices may differ, it is not apparent how those differences would explain the contradictory findings.

In the Meyers and Greenberg study, 110 of the 271 patients with unipolar major depression were excluded because of medications, active medical illness, or cognitive impairment that might have caused the depression. These concurrent conditions, however, are characteristic of older patients. We excluded patients whose depression was *caused* by drugs or medical illness but found a definite medical etiology in only five cases. It is possible that our general hospital sample included more patients with active medical illness, but when these patients were excluded, age at onset was actually younger in the delusional patients. We acknowledge the difficulty in distinguishing dementia with depressive features from major depression with concurrent dementia (10), but when patients with any evidence of dementia were excluded, our findings remained unchanged. Concurrent medical illness or dementia did not appear to explain the differences in our data.

Our finding of no significant difference in age at onset in delusional and nondelusional patients is similar to several prior studies that used mixed age samples (3–7). It suggests that late-onset depression does not appear to be distinct, with respect to delusional status, or associated with cognitive disturbance that results in a higher frequency of delusions.

REFERENCES

1. Meyers BS, Kalyam B, Mei-Tal V: Late onset delusional depression: a distinct clinical entity. *J Clin Psychiatry* 1984; 45:347–349
2. Meyers BS, Greenberg R: Late-life delusional depression. *J Affective Disord* 1986; 11:133–137
3. Nelson JC, Bowers MB: Delusional unipolar depression: description and drug response. *Arch Gen Psychiatry* 1978; 35:1321–1328
4. Charney DS, Nelson JC: Delusional and nondelusional unipolar depression: further evidence for distinct subtypes. *Am J Psychiatry* 1981; 138:328–333
5. Frances A, Brown RP, Kocsis JH, et al: Psychotic depression: a separate entity? *Am J Psychiatry* 1981; 138:831–833
6. Glassman AH, Roose SP: Delusional depression: a distinct clinical entity? *Arch Gen Psychiatry* 1981; 38:716–719
7. Frangos E, Athanassenas G, Tsitourides S, et al: Psychotic depressive disorder, a separate entity? *J Affective Disord* 1983; 5:259–265
8. Conwell YC, Nelson JC, Kim K, et al: Elderly patients admitted to the psychiatric unit of a general hospital. *J Am Geriatr Soc* 1989; 37:35–41
9. Spitzer RL, Endicott J: Schedule for Affective Disorders and Schizophrenia, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1977
10. Devanand D, Nelson JC: Concurrent depression and dementia: implications for diagnosis and treatment. *J Clin Psychiatry* 1985; 46:389–392

CSF GABA in Caregiver Spouses of Alzheimer Patients

Nunzio Pomara, M.D., Dennis Deptula, Ph.D., Matthew P. Galloway, Ph.D.,
Peter A. LeWitt, M.D., and Michael Stanley, Ph.D.

The authors studied CSF γ -aminobutyric acid (GABA) in 14 Alzheimer patients and nine age-matched normal subjects. The five normal subjects who were wives of the demented patients had higher CSF GABA concentrations than the four normal subjects without demented spouses. (Am J Psychiatry 1989; 146:787-788)

In contrast to the marked alterations in the cholinergic, somatostatin, and corticotropin-releasing factor neuronal systems, substantial loss of neurons that contain γ -aminobutyric acid (GABA) does not accompany Alzheimer's disease (1). Nevertheless, Alzheimer's disease has been associated with low density of cortical GABA_B receptors (2), substantially low GABA uptake in biopsied brain tissue (3), and low concentrations of GABA in the brain (4) and in CSF (5). Therefore, we decided to compare CSF GABA concentrations of patients with probable Alzheimer's disease and age-matched normal subjects. During data analysis, we noted that the demented patients' caregiver spouses who had been included among the normal subjects exhibited a markedly higher mean CSF GABA concentration than the normal subjects who were not caring for a demented spouse.

METHOD

We studied 14 demented patients (seven women, seven men) and nine age-matched normal subjects (seven women, two men). The patients met NINCDS-ADRDA criteria for probable Alzheimer's disease and DSM-III criteria for primary degenerative dementia. Diagnosis was based on psychiatric evaluation, physical examination, laboratory investigations, and head CT scans. The patients tended to be moderately demented, having a mean \pm SD Global Deterioration Scale score of 4.6 ± 0.6 and a mean \pm SD Folstein Mini-Mental State

score of 17.1 ± 3.9 , and 12 of the 14 had a presenile onset. The nine normal subjects underwent physical examinations and routine laboratory investigations, which revealed no major medical, neurological, or psychiatric disorders. Five of the nine normal subjects were wives of the Alzheimer's disease subjects. None of the 23 subjects were taking psychotropic medications or had a history of neuroleptic or antidepressant treatment. Although there was a higher female to male ratio among the normal subjects than among the patients, chi-square test indicated this difference was not significant.

Before a subject's participation, the procedure was fully explained and informed consent was obtained. All 23 subjects were admitted to the inpatient service at the Lafayette Clinic 1 day before the lumbar punctures. After overnight bed rest and fasting, the subjects underwent lumbar punctures between 9:00 a.m. and 10:00 a.m. in the standard fashion with the subject in the lateral decubitus position. CSF (approximately 20 cc) was collected on ice in a standardized manner and frozen at -70°C . Aliquots from a pooled specimen of the 3rd-17th ml were used for determination of GABA concentrations with a highly sensitive and specific radioreceptor assay previously described by Enna et al. (6). Homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations were determined by high performance liquid chromatography; the sensitivity of the assay was 1 ng/ml of CSF, and the specificity was analytically determined. There were no interfering peaks that appeared on the chromatograph. 3-Methoxy-4-hydroxyphenylglycol (MHPG) was separated by gas chromatography and identified and quantified by mass spectrometry of specific ion fragments; the sensitivity was approximately 0.1 ng/ml.

RESULTS

Although the mean CSF GABA concentration of demented patients was 28% lower than that of the normal subjects (table 1), a nonparametric Mann-Whitney test did not reveal statistically significant differences between Alzheimer and normal subjects in CSF GABA concentrations ($U=82.50$, $N=23$, $p>0.05$). Additionally, GABA concentrations did not significantly correlate with severity of dementia as measured by scores on the Mini-Mental State and the Global Deterioration Scale.

The five spouses of Alzheimer's disease patients had

Received March 15, 1988; revision received Oct. 20, 1988; accepted Dec. 1, 1988. From the Lafayette Clinic and Wayne State University School of Medicine, Detroit, Mich. Address reprint requests to Dr. Pomara, The Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY 10962.

The authors thank S.J. Enna, Ph.D., for determination of CSF GABA concentration.

Copyright © 1989 American Psychiatric Association.

TABLE 1. Age and CSF GABA Concentration in Patients With Probable Alzheimer's Disease and Normal Subjects

Subjects	Age (years)		GABA (pmol/ml)	
	Mean	SD	Mean	SD
Probable Alzheimer's disease (N=14)	60.7	9.4	154.9	64.3
Normal (N=9)	64.0	11.8	216.4	101.5
With demented spouse (N=5)	63.6	11.7	293.0 ^a	58.9
Without demented spouse (N=4)	64.5	13.8	120.8	29.4

^aSignificantly higher than in normal subjects without demented spouses (U=0.0, p<0.03).

a significantly higher mean concentration of GABA in the CSF than the four normal subjects without demented spouses (table 1). When we examined possible confounding variables, the higher CSF GABA concentration in spouses of Alzheimer's disease patients could not be explained by differences in age, weight, height, or gender (7) between the groups. Additionally, the higher GABA concentration in spouses of Alzheimer's disease patients was not accompanied by alterations in CSF concentrations of 5-HIAA, HVA, or MHPG.

DISCUSSION

Alterations in GABA neurotransmission have been postulated to play a role in the pathophysiology of a number of disorders such as Huntington's disease, tardive dyskinesia, epilepsy, Parkinson's disease, depressive illness, and anxiety. Abnormalities in cortical GABA-containing neurons (3, 4) and CSF GABA concentrations (5) have also been described in Alzheimer's disease. The tendency for our Alzheimer's disease patients to have a lower mean CSF GABA concentration than our normal subjects might suggest that some cortical GABA-containing neurons are degenerating in this disorder; the nonsignificance of the finding might be due to the fact that these cortical neurons constitute a small percentage of the total GABA-containing neurons in the CNS. Alternatively, the statistically nonsignificant lower than normal mean concentration of GABA in this small sample of mildly to moderately impaired patients might suggest that CSF GABA is not altered in the early stages of Alzheimer's disease.

The dramatically high mean CSF GABA concentration in the caregiver spouses of the demented patients appears to be selective since it was not accompanied by high levels of HVA, 5-HIAA, or MHPG. We do not know the neurochemical basis for the high mean concentration of CSF GABA in these caregiver spouses. Many factors, such as improper handling and storage of CSF samples, comparisons of different CSF fractions, differences in the total CSF volume, prior exposure to psychotropic medications, can influence CSF GABA concentration. Although these factors cannot be completely ruled out, our adherence to a standard procedure before and during lumbar punctures, use of the same CSF fraction, imme-

diating freezing of CSF, and exclusion of individuals taking psychotropic drugs make it unlikely that they are the only reasons for the higher mean CSF GABA concentration in the caregiver spouses of the demented patients.

Because providing continuous home care and supervision to a demented individual is generally thought to be extremely stressful for the caregiver spouse (8), the higher than normal mean CSF GABA concentration in our caregiver spouses may be related to stress. There is a body of literature that is consistent with the possible role of GABA in the response to stress. The application of various types of acute stressors to animals has been associated with alterations in GABA concentration (9) and increases in the activity of the GABA receptor-gated chloride channel (10) in the brain. Moreover, it has been suggested that "alterations in GABAergic 'inhibitory tone' may serve to attenuate the physiological and perhaps cognitive components of stress" (11). Therefore, the high mean CSF GABA concentration in our presumably stressed, yet seemingly well-functioning caregivers of demented spouses may represent an adaptive response to chronic stress.

To our knowledge, no studies in humans have examined the effect of acute and chronic stress on GABA concentrations. Our preliminary, incidental, and significant finding suggests that further investigation of the relationship between stress response and GABA in humans is warranted.

REFERENCES

1. Rossor MN, Garrett NJ, Johnson AL, et al: A post-mortem study of the cholinergic and GABA systems in senile dementia. *Brain* 1982; 105:313-330
2. Chu DCM, Denney JB, Young AB: Cortical GABA_B and GABA_A receptors in Alzheimer's disease: a quantitative autoradiographic study. *Neurology* 1987; 37:1454-1459
3. Hardy J, Cowburn R, Barton A, et al: A disorder of cortical GABAergic innervation in Alzheimer's disease. *Neurosci Lett* 1987; 73:192-196
4. Ellison DW, Beal F, Mazurek MF, et al: A post-mortem study of amino acid neurotransmitters in Alzheimer's disease. *Ann Neurol* 1986; 20:616-621
5. Zimmer R, Teelken AW, Trieling WB, et al: γ -Aminobutyric acid and homovanillic acid concentration in the CSF of patients with senile dementia of the Alzheimer's type. *Arch Neurol* 1984; 41:602-604
6. Enna SJ, Wood JH, Snyder SH: γ -Aminobutyric acid (GABA) in human cerebrospinal fluid: radio-receptor assay. *J Neurochem* 1977; 28:1121-1124
7. Gold BL, Bowers MB, Roth RH, et al: GABA levels in CSF of patients with psychiatric disorders. *Am J Psychiatry* 1980; 137: 362-364
8. Zarit SH, Orr NK, Zarit JM: *The Hidden Victims of Alzheimer's Disease: Families Under Stress*. New York, New York University Press, 1985
9. Yoneda Y, Kanmori K, Ida S, et al: Stress-induced alterations in metabolism of γ -aminobutyric acid in rat brain. *J Neurochem* 1983; 40:350-356
10. Schwartz RD, Wess MJ, Labarca R, et al: Acute stress enhances the activity of the GABA receptor-gated chloride ion channel in brain. *Brain Res* 1987; 411:151-155
11. Hommer DW, Skolnick P, Paul SM: The benzodiazepine/GABA receptor complex and anxiety, in *Psychopharmacology: The Third Generation of Progress*. Edited by Meltzer HY. New York, Raven Press, 1987

Self-Cutting After Rape

Gail S. Greenspan, M.D., and Steven E. Samuel, Ph.D.

The authors present three cases of women who began to cut themselves superficially after they had been raped. To the authors' knowledge, no such findings have been reported in the current literature on short- and long-term effects of rape.

(Am J Psychiatry 1989; 146:789-790)

The psychological effects of rape have been studied and described in the psychiatric literature by several authors, particularly in the past decade. This literature began with the work of Burgess and Holmstrom (1), who first described the "rape trauma syndrome." Symptoms common to this syndrome are anxiety, depression, disturbances in functioning, loss of appetite, insomnia, nightmares, flashbacks, sexual dysfunctions, social withdrawal, prolonged feelings of guilt or shame, and a number of changes in lifestyle. Nadelson et al. (2) found that 40%-50% of rape victims reported intermittent depressions and sexual difficulties. Using improved research methods, Kilpatrick et al. (3, 4) have presented an increasingly clear picture of the aftermath of rape.

To our knowledge, there have been no published reports of self-cutting after rape. By "self-cutting," we are referring to the act of superficially lacerating the skin, usually of the wrist or forearm, with a sharp object and inducing blood flow. In our work on a general psychiatric unit of a general medical teaching hospital, we have encountered several such cases. In all of these cases, self-cutting was a predominant symptom, but the history of sexual assault was not always immediately evident. After a full history was obtained, it became clear that the self-cutting was part of a post-traumatic stress disorder (PTSD) and that it began after a rape. Neither of the women in the first two cases we present had a history of incest or child abuse or had been given a diagnosis of a personality disorder or a major depressive episode. The woman in the third case had a similar PTSD symptom pattern, and the onset of her cutting also followed rape, but she had a childhood

history of incest and a diagnosis of borderline personality disorder.

CASE REPORTS

Case 1. Ms. A, a 19-year-old white woman, was first hospitalized after an episode of wrist cutting. She had been in therapy for 3 months; her initial symptoms included severe anxiety, recurrent nightmares, a compulsion to bathe, and intermittent amnesic periods. She reported having been violently raped by the same assailant several times, approximately 8-9 months before she started therapy. The rape experiences were accompanied by threats of death were she ever to tell.

At first, Ms. A had been unable to tell of her episodes of self-cutting. During a typical episode she would make several horizontal slashes on one forearm, using a piece of glass, the sharp edge of a can, or a knife. The cuts always drew blood but did not require sutures. During one particularly disturbed period of her life, she cut her upper thigh with a knife. She consistently reported the absence of pain during and after the self-cutting. The secrecy that surrounded this behavior seemed to parallel the silence she felt she must maintain about the rapes. She said that cutting her arm provided a release for unbearable tension that built up as part of a rape-related flashback. While it is not our purpose in this paper to explore the complex psychodynamic meanings of the cutting, it clearly expressed a terrifying and tremendous rage that she had suppressed and turned inward.

This young woman had no prior psychiatric history. She had been a bright, outgoing student who had excelled both in school and in many extracurricular activities. She had dated in high school and reported having had a normal sexual relationship with a boyfriend from age 17 to 18. She had no history of depression, drug abuse, promiscuity, or self-mutilation before the rape.

Case 2. Ms. B, an 18-year-old black woman, was admitted to the hospital for evaluation and treatment after an episode of cutting her arm with a piece of glass. Examination of the affected forearm revealed several overlapping and superficial cuts, approximately 2-3 cm in length; sutures were not necessary. She reported that a small amount of blood had flowed immediately after her cutting. She initially admitted to suicidal ideation, feeling miserable, and the recent onset of insomnia, nightmares, and social withdrawal. Two weeks before this episode of self-cutting she had first superficially lacerated her arm but had told no one.

During her first week of hospitalization, Ms. B was able to gain support from hospital staff. However, she was clearly more uncomfortable and withdrawn around the male psychiatric resident and nurses than with the female attending psychiatrist and nurses. She gradually opened up to a female

Received July 26, 1988; revision received Dec. 7, 1988; accepted Dec. 20, 1988. From the Department of Psychiatry, Jefferson Medical College. Address reprint requests to Dr. Greenspan, Jefferson Medical College, 1558 Thompson Bldg., 111 South 11th St., Philadelphia, PA 19107.

Copyright © 1989 American Psychiatric Association.

staff member about the events that had precipitated her hospitalization. With considerable trepidation, she admitted to having been raped by an unknown assailant 5–6 months before this admission. She was warned by her attacker to keep quiet about the rape. She reported many of the typical symptoms of rape trauma syndrome and a growing sense of shame, dirtiness, self-blame, and a wish to die as a means of escape from this misery.

Ms. B had attempted suicide 2 years earlier; she took an overdose of her seizure medication after being separated from the foster family with whom she had grown up. Our understanding of her behavior at the time of this earlier event is more consistent with an adjustment disorder with depressed mood (in reaction to a sudden and traumatic separation from her foster family) than with a major depressive episode. She was later reunited with the family. Ms. B reported a return to her usual mood and behavior in the ensuing period, until the rape. After beginning to talk about her traumatic experience, she expressed a desire to continue in psychotherapy after discharge from the hospital.

Case 3. Ms. C, a 32-year-old white woman, was seen in outpatient supportive group therapy for victims of rape and incest. She had been hospitalized a number of times for self-cutting. She stated that she first started to cut herself after she had been raped at the age of 18. When she cut herself, she usually used a knife or razor and made multiple horizontal 4–5-cm slashes on her forearms and/or thighs. Occasionally these required sutures. Her forearms were badly scarred; she always wore long sleeves and long skirts, in part to cover the multiple cuts. The occurrence of blood flow was an important signal to her to stop cutting. To our knowledge, she never suffered a major blood loss because of the cutting. She stated clearly that her episodes of self-cutting were never actual suicide attempts but, rather, her only means to relieve overwhelming and painful tension. She had been raped several times in her adult life, by different assailants. She reported bouts of anxiety, flashbacks, insomnia, frequent urges to bathe, sexual inhibitions, and weight gain since the assaults. Ms. C felt that her acts of self-cutting were intimately related to being raped and frequently felt frustrated by her unsuccessful mastery of her intense feelings.

DISCUSSION

The literature on aggression after trauma has only recently begun to address self-destructive behaviors (5, 6). There have been suggestions that individuals who have experienced child abuse or incest reveal more marked difficulties in expressing aggression (7). Our observations of the more general psychiatric population of self-cutters certainly bear this out. In addition, more severe psychopathology after rape is found in victims of prior sexual assault, as has been mentioned by Santiago et al. (8) and others.

The type of self-mutilation we have described—a

superficial cutting of the forearm, often occurring in a state of depersonalization—seems to resemble the “delicate cutting” described by Pao (9). In fact, the cutting represents an attempt to end these frightening depersonalized feelings.

While we have reported only a few cases, it is our impression that this phenomenon may be underreported, because of a few factors. First of all, when patients come to crisis centers with self-inflicted non-lethal injuries, they are all too often diagnosed as borderline in an almost knee-jerk response. Needless to say, labeling a patient “borderline” in no way explains the self-cutting and may in fact unduly influence the examiner to avoid gathering additional, more relevant information about the cutting. The unfortunate outcome, in many cases, is the obscuring of symptoms of PTSD.

Second, taking a sexual history that includes traumatic sexual events is not routine in all initial psychiatric interviews. Sexual abuse is one of the most likely events to be consciously suppressed or unconsciously repressed. House and Thompson (10) suggested some basic steps for the initial psychiatric evaluation of self-injuring patients. We recommend including sensitive questioning about rape (and incest) as part of the initial psychiatric evaluation, especially with patients who cut themselves.

We would welcome additional reports from colleagues who have seen patients who start self-cutting after rape.

REFERENCES

1. Burgess AW, Holmstrom LL: Rape trauma syndrome. *Am J Psychiatry* 1974; 131:981–986
2. Nadelson CC, Notman MT, Jackson H, et al: A follow-up study of rape victims. *Am J Psychiatry* 1982; 139:1266–1270
3. Kilpatrick DG, Veronen LJ, Resick PA: The aftermath of rape: recent empirical findings. *Am J Orthopsychiatry* 1979; 49:658–669
4. Kilpatrick DG, Veronen LJ, Best CL: Factors predicting psychological distress in rape victims, in *Trauma and Its Wake*. Edited by Figley C. New York, Brunner/Mazel, 1985
5. Carmen E(H), Rieker PP, Mills T: Victims of violence and psychiatric illness. *Am J Psychiatry* 1984; 141:378–383
6. Von der Kolk B, Greenberg S: The psychobiology of the trauma response: hyperarousal, constriction, and addiction to traumatic response, in *Psychological Trauma*. Edited by Von der Kolk B. Washington, DC, American Psychiatric Press, 1987
7. Stone M: A psychodynamic approach: some thoughts on the dynamics and therapy of self-mutilating borderline patients. *J Personality Disorders* 1987; 1:347–349
8. Santiago JM, McCall-Perez F, Gorcey M, et al: Long-term psychological effects of rape in 35 rape victims. *Am J Psychiatry* 1985; 142:1338–1340
9. Pao PN: The syndrome of delicate self-cutting. *Br J Med Psychol* 1969; 42:195–206
10. House R, Thompson T: Acute psychiatric evaluation of self-injuring patients. *Psychosomatics* 1985; 26:845–851

Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

DISORDERS OF AGING

Handbook of Clinical Gerontology, edited by Laura L. Carstensen, Ph.D., and Barry A. Edelstein, Ph.D. New York, Pergamon Press, 1987, 399 pp., \$75.00.

A central theme of adult development is the crisis precipitated by the recognition and acceptance of our finiteness in time and the inevitability of personal death. This relentless progression through old age toward death is described to Kate by King Henry V (Act V, Scene ii, line 155):

A good leg will fall; a straight back will stoop; a black beard will turn white; a curled pate will grow bald; a fair face will wither; a full eye will wax hollow; but a good heart, Kate, is the sun and the moon; or, rather, the sun, and not the moon; for it shines bright and never changes, but keeps his course truly.

What is this quiddity called "old age"? Hippocrates believed old age began at 55 years. The tragic character Lear was "fourscore and upward" when he began his final journey toward decrepitude and death. Psalm 90:10 puts old age at 70:

The days of our years are threescore years and ten; and if by reason of strength they be fourscore years, yet is their strength labour and sorrow; for it is soon cut off, and we fly away.

Yet, independent of this heterogeneity in the notion of "old age," we must still address the clinical needs of our ever-increasing aged population. Gerontologists have long recognized the manifold and conflating variables that influence both the nature and course of the journey through late life. To help clinicians address the multiple factors involved with the medical and psychological problems of the elderly, Drs. Carstensen and Edelstein have edited this *Handbook of Clinical Gerontology*. It is written for the student interested in the broad issues of clinical gerontology and for the "seasoned clinician" who is searching for a "comprehensive resource on which one can rely for an up-to-date discussion of medical, social, or mental health problems, both within and outside one's specialty area."

The name "handbook" may be a misnomer. By my understanding, a handbook is small enough to be held in the hand, is primarily written for practitioners, and is expected to get constant revision and reference. This one is divided into five parts with a total of 28 well-referenced chapters by different authors, an author index, a subject index, and a collection of brief author biographies. It is 36 cm by 18 cm by 3 cm and weighs 1.01 kg.

Part one reviews several theories of biological aging, discusses cytogerontology as it relates to aging at the cellular level, outlines normative age-related physical and psychological changes, and underscores the importance of increas-

ing the environmental variety and human social milieu of institutions.

Part two provides an introduction to the mental health problems attending old age. Included are discussions of the geropsychiatric aspects of the diagnosis and treatment of depression, dementia, paranoia, alcohol abuse, and sexual dysfunction.

Part three confronts and reviews many of the issues involved with geriatric medicine as it pertains to cancer management, cardiovascular illness, orthopedic problems, and the omnipresent use of medication. The chapter on medications has a particularly useful disquisition on pharmacodynamics and pharmacokinetics, adverse drug interactions, and the diminished capacity of homeostatic mechanisms in the geriatric population.

Part four focuses on the major behavioral problems in old age that often emerge from physical insult, including functional disabilities that compromise interaction with the social structure. Among these are pain, wandering and disorientation, dependency, sleep disturbances, urinary incontinence, family problems, and the cognitive, psychosocial, and behavioral sequelae of cerebrovascular accidents.

Finally, part five reflects some of the more abstract social issues confronting the elderly. Included here are chapters on the concept of social support, the nature of bereavement, the notion of a place called home, gerontic issues of the black elderly, geropolitics and the Gray Panthers, and ethical considerations with respect to competence, autonomy, research, and therapy.

Although this tome is extremely well written and well edited (I found only seven typographical peccadilloes in more than 400 pages of text), I had a disquieting sensation of déjà vu while reading it. There is nothing new or exciting here. My disquietude is partially explained by the rapid turnover of scientific information and concurrent advances in geriatric medicine. Not discussed at all are recent advances in Alzheimer's disease research, which include the suggestion of the need to prevent amyloid protein accumulation in the brain and that either a virus or a gene deficit for controlling an enzyme for amyloid proteolysis may be involved. Similarly, most of the chapter references are from 1985 or earlier. I can readily sympathize with the editors' need to start somewhere in time and to limit the scope of included topics. However, as this handbook grows with constant revision, I would hope that additional topics such as neglect and abuse of the elderly, emergency geroneuropsychiatry and medicine, the economic impact of an aging population on resource allocation and life-prolonging medical interventions, gerolegal problems, and geriatric epidemiology would be included.

Whether we personally confront old age "withered like an old apple-john" or end our days like "the wonderful one-hoss shay" of *The Deacon's Masterpiece*, as clinicians we cannot forsake the clinical needs and concerns of our geriatric patients. Updated compendia like the *Handbook of Clinical Gerontology* not only will add to our knowledge and clinical acumen but may also help defuse the growing

time bomb of ageism. To paraphrase Rabbi Nahman of Bratslav, one can gauge a country's greatness by its treatment of the aged.

MICHAEL F. HEIMAN, M.D.
Napa, Calif.

Treating the Elderly With Psychotherapy: The Scope for Change in Later Life, edited by Joel Sadavoy, M.D., and Molyn Leszcz, M.D. Madison, Conn., International Universities Press, 1987, 365 pp., \$37.50.

This excellent book has many useful ideas in its text and bibliographies. There are also name and subject indexes, an instructive preface that explains the origins of the book's material, and a superb foreword by Irvin D. Yalom, M.D., which is almost a book review in itself. Three of Dr. Yalom's points are dealt with in depth in the text. 1) The book dispels the myths spawned by contemporary ageism and by archaic psychoanalytic concepts of human development. 2) It does not present the elderly as untreatable people with rigid, inelastic personality structures. 3) The age-specific dynamic theme of loss runs unsilently and deeply throughout the book; loss of possibility is the most grievous.

The book has 11 chapters divided into three sections: General Psychodynamic Perspectives, Manifestations of Psychopathology, and Specific Psychotherapeutic Modalities. Dr. Sadavoy's chapter seven is the spine of the book.

In the first chapter, George H. Pollock, M.D., APA's immediate past-president, discusses the mourning process and the subsequent liberation process, describes four main considerations in working with older adults (antecedent psychopathology, situational crises, the effects of organic health status on the psyche, and personal capacities that foster successful psychoanalytic treatment), and calls to our attention some interesting ideas about fear and death. "What seemingly concerns . . . older patients the most is fear of pain and suffering, helplessness and hopelessness, isolation and loneliness, physical and mental impairment, loss of competency and adequacy, and the need to rely upon those who may abandon them. Unlike young patients, the elderly do not fear death. At times they welcome it as a relief from pain and anguish. Death may be a completion . . . or even a freedom."

I think that Dr. Pollock's comments on death are more likely to fit the case of the normal person who feels he or she has completed the full life cycle. For those persons who have not done so, the angst and anger are proportional to the degree they feel that they have been cheated or deprived by the forces of life. Patients with personality disorders are the least prepared for aging, loss of action outlets, and institutionalization.

The chapter by Dr. Sadavoy, "Character Disorders in the Elderly," is impressive in its depth of information. His 58-page overview, when added to the 62-page chapter by Henry Krystal, M.D., "Impact of Massive Psychic Trauma," represents more than one-third of the text. I conclude that these authors find that for many persons institutionalization is not a satisfying dependency gratification but a massive psychic trauma. Dr. Sadavoy tells us how the institutionalized elderly person burdened with a personality disorder may have inner tensions that build to unbearable levels. This results in aberrant interactional patterns and exacerbation of narcissistic defenses, hypochondriasis, and depressive withdrawal. Dr. Krystal points out that massive psychic traumatization has dynamics and a history of its own and that the therapy and

dynamics of neuroses may not be applicable to these kinds of psychic trauma. He states that people are severely damaged when their physical safety is threatened, their autonomy is violated, and they are subjected to oppression and humiliation. Apparently this is how many elderly persons feel about having to leave their own dwelling and being placed in a nursing home. The change in circumstances, the confinement, and the intensity of the closeness all compare unfavorably with what existed before, and this combined with the stress factors described by Dr. Sadavoy are just too much.

The exaggerated helplessness syndrome, described in a chapter by Lawrence Breslau, M.D., is a major coping approach of some elderly people. Paranoid phenomena are another; these are described by Adrian Verwoerd, M.D. Chapters on different aspects of therapy are provided by Jerome M. Grunes, M.D., Martin A. Berezin, M.D., Ralph J. Kahana, M.D., Lawrence W. Lazarus, M.D., and Lesley Groves, M.S., Etta Ginsberg McEwan, M.S.W., and Molyn Leszcz, M.D. These range from brief psychotherapy to long-term psychotherapy and cover psychoanalytic psychodynamics, family therapy, and group therapy.

Although the book suffers somewhat from being a synthesis of separate presentations, and one could argue for a different chapter sequence, the chapter sequence used is fine and the interrelatedness of the material makes the synthesis not difficult. Indeed, this excellent book could serve as a text on the treatment of the nation's elderly for teaching psychiatrists in the second or third year of training and for updating the knowledge of those already practicing. It only touches on the problems encountered in guardianship and advocacy for proper standards of care for the elderly who can no longer maintain completely independent function. Any second edition should contain a chapter on these forensic aspects.

The quality of the case descriptions in this book is truly outstanding. They are the best in terms of diagnosis, treatment, and program presentation that I have encountered in more than 24 years of study. In the hands of an experienced psychiatrist who has done both inpatient and outpatient treatment, uses team approaches, and is willing to look for the psychodynamic diagnosis as well as the nosological diagnosis, these case descriptions can serve as marvelous teaching vehicles for both acute and long-term treatment. They will give support to those who feel pressured by the brief therapy, health maintenance organization, and rapid admission-rapid discharge movements. Both short-term and long-term treatment opportunities are needed, and this book can teach how to conduct both.

LAWRENCE K. RICHARDS, M.D.
Champaign-Urbana, Ill.

ParentCare: A Commonsense Guide for Adult Children, by Lissy Jarvik, M.D., Ph.D., and Gary Small, M.D. New York, Crown, 1988, 299 pp., \$19.95.

This book has universal appeal. We all have or had parents we care about in one way or other, and more and more of us find ourselves having to assume some kind of responsibility for our parents, at times somewhat similar to the kind of responsibility they had for us as children. Our professional literature abounds with descriptions of the theory and practice of child development and parenting, but *ParentCare* is in the avant-garde of literature pertaining to the development of middle-aged children as they adapt to their parents' decline in today's society. *ParentCare* reflects the authors' em-

pathy for those involved in this developmental task. In a highly readable conversational style, they make a concerted effort to assist adult children to master intergenerational situations that are often fraught with conflict and frustration.

Each chapter of this book is elegantly introduced by a pertinent quotation from our sages, poets, and philosophers. Historical derivatives and phonetic spellings of medical terms are provided and explicit explanations given for the lay reader.

Each theoretical or practical point is demonstrated with poignant and lively first-name vignettes that give the reader the impression of having been there and getting to know the situation in a very personal way. The authors bring their professionalism and wealth of experience to the task of educating their readership to become active listeners and effective negotiators on behalf of themselves and their parents.

The authors discuss the defense mechanisms explored by Anna Freud that occur in health and pathology in children. They translate these mechanisms for the lay person in a schematic way to show how the problem-solving capacity can be enhanced and how blocks to further ego development can be alleviated in the middle years when children are faced with the care of their parents. The book is preventive in tone and focuses on maintaining intergenerational mental health and relationships.

Each chapter covers a range of problems that can occur during aging. Not only do the authors share their resourcefulness, they also invite the reader to fill in a commonsense checklist (p. 24) to make the recommendations they give relevant to the reader's situation. There is also a fill-in form to show the parallels between the parents' lifelines from birth to death and those of the adult child caregivers (p. 125).

Theory and practice are well blended in this book. It touches on many of the experiences of parents that their adult children often react to strongly, such as the parents' retirement, relocation, widowhood, remarriage, illness, disability, and financial, sexual, and nutritional concerns. It also discusses other losses, including death and dying. The authors invite the reader to go through the halls of a nursing home as though with a recorder in hand capturing sight, sound, and odor.

Historical perspectives are used to assist in overcoming bias, and psychodynamic perspectives are used to bring expectations and realities closer together. The appendixes are full of useful information and admonitions. The caregiver, so often a daughter or daughter-in-law, who has read *Parent-Care* may come across as "knowing it all," or at least being able to find it all out (even if only by following the authors' recommendations not to hesitate to contact the physician day or night). The appendixes focus on topics such as Alzheimer's disease, descriptions of the various health care professionals, side effects of antidepressants, durable power of attorney, the living will, and a listing of resources in geriatric medicine, including a state-by-state listing of geriatric psychiatry fellowship training programs.

This book, although written for the adult child, is recommended for a wide audience. Professional providers of care need to keep up with the consumers of health and mental health care. It is a welcome addition to any psychiatrist's office, psychiatric library, general hospital library, and any reading list of courses for gerontologists, medical students rotating through psychiatry, and residents in any medical specialty, especially psychiatry. The ever-burgeoning number of family practitioners should have a copy in their offices to learn when psychiatric referrals are indicated—when the problem-solving capacity of the adult child is impaired in

dealing with the three-generational concerns of the sandwich generation. Both families and clinicians can benefit from reading *Parent-Care*. Psychiatrists should recommend it to their colleagues in other medical specialties.

MARION Z. GOLDSTEIN, M.D.
Buffalo, N.Y.

DISORDERS OF CHILDHOOD

Handbook of Autism and Pervasive Developmental Disorders, edited by Donald J. Cohen and Anne M. Donnellan. New York, John Wiley & Sons, 1987, 757 pp., \$55.00.

As a child psychiatrist working in the real agora of patients, parents, school administrators, and politicians, I daily see in each child with autism or other pervasive developmental disorder the most strikingly obvious reason why some of us in psychiatry develop a recurrent ambivalence toward an omnipotent and just God. Perhaps it is our medical school training, heavily influenced by William Osler's demanding cold precision in the handling of our patients, or the paranoiac exposure to Melvin Belli prototypes that foster these fears, but each such child certainly illustrates in sharp relief what Lorna Wing so understatedly said about these disorders: "Nature never draws a straight line without smudging it."

In their preface, the editors state that "a handbook is not only a summary of what is known, but also a guide to areas that are poorly or not at all charted." This handbook achieves all that and more. It probes, challenges, and tests to the utter limits of each research finding's possibilities the untested boundaries of each discipline's perimeter. The 54 chapters of the book are divided into four sections. The feat of getting 76 contributors and 30 members of the editorial board, coming from such normally adversarial fields as law, communication disorders, psychology, vocational rehabilitation, pediatrics, neurology, and "the entire scope of biomedical sciences," to agree to talk with each other under the umbrella of a tight and uniform editorial writing style is awesome in and of itself.

In the Philippines, there is a practice called the *lauriat* in which a host displays respect for a very honored guest by offering a cornucopia of apparently unrelated dishes numbering no less than eight at a time. The feast usually lasts 4 hours, at least. Each dish is so unique and so filling that no gourmand leaves unsated, and each gourmet sits awed by the challenge to the more than 200 taste buds each of us is supposed to possess. This is how I felt as I savored this *lauriat* for 4 weeks. From the sobering admission that autism and pervasive developmental disorders are lifelong and devastating to the hopeful taste of new research breakthroughs and successful intervention and advocacy strategies, I ended the banquet nourished and energized.

The book starts out by reviewing known "facts" as well as the contradictions of such facts. It then discusses misleading and destructive belief systems, such as "refrigerator mothers" and "unreachable robots." From Kanner to Rutter, like a wise and compassionate avuncular tour guide, the book knowingly and with piquant humor treats us to more than a cook's tour of the blind alley paths of yesterday to the sudden panorama opened up by biomedical, language, and educational research. Although Campbell's chapter on psychopharmacology is a bit weak and tentative, the overall tenor

of this handbook is one of robust enthusiasm that leads us to a more enlightened understanding not only of pervasive developmental disorders but of the human being in general. Already, my approach to my adult patients has been markedly affected by the insights drawn from the chapters on cognitive and neurochemical research and those on advocacy and legal strategies. It was striking for me to discover that so many of my difficult-to-reach adult patients had indeed suffered from undiagnosed pervasive developmental disorders in childhood. I am now treating a whole family of patients formerly treated in various institutions as having simple affective acting-out disorders. I serendipitously discovered that these patients had pervasive developmental disorders and psychomotor seizure disorders; they are responding quite nicely to divalproex sodium.

The chapters written by the authors in the field of education deserve to be singled out as outstanding, not only in their obvious scholarlyness but also for their admirable demonstration over the years that treating the human being with any problem is not just the province of the "medical model" of old. Such treatment requires a team approach that includes not only the patient and the parents but also a vast support system. As monopolists obsessed with our own territorial imperative, we psychiatrists have refused or were afraid to tap this support system. The chapter by Frank Warren, Associate Director of Community Services for Autistic Adults and Children in Rockville, Md., describing the evolution of the Training and Education for Autistic and Other Children With Communication Handicaps Program, starting with its inception by a small group of parents in North Carolina in 1968, is profoundly humbling, entertaining, and effective. This chapter should be read by all parents and professionals in the helping professions because Warren shows us, through clear, concrete strategies, how individuals and organizations can overcome being insouciant, withdrawn, or hopeless and be converted into powerful forces to be reckoned with. This chapter is a hopeful and pragmatic workbook.

I unabashedly recommend this book for everyone—not just for collecting dust but for daily reference. This is an action book, and I am actively promoting it through speeches in our local churches, parent-teacher association meetings, and local area education agencies, advocacy groups, and classrooms.

TRUCE T. ORDONA, M.D.
Davenport, Iowa

The Hyperactive Child, Adolescent, and Adult: Attention Deficit Disorder Through the Lifespan, by Paul H. Wender, M.D. New York, Oxford University Press, 1987, 150 pp., \$6.95 (paper).

Attention deficit disorder is one of the more important psychiatric disorders of childhood. It is important because of its prevalence in the general population and because of its prevalence in children who are referred for evaluation to child psychiatrists and other mental health practitioners. Moreover, the untreated outcome of attention deficit disorder in childhood is often continuing problems in adolescence and perhaps persistence into adult life.

In 1973, Paul Wender, one of the leading researchers in the area of attention deficit disorder, authored *The Hyperactive Child* (1) to provide parents with information about the nature, causes, and treatment for what at that time was called

the hyperkinetic syndrome. In 1978, with Esther Wender, he published a revised version of the book (2), which contained up-to-date information about the learning problems often seen in children with this disorder.

Now Wender has produced *The Hyperactive Child, Adolescent, and Adult: Attention Deficit Disorder Through the Lifespan*, which is a continuing update including more information about the adolescent and adult outcome of this disorder. The current book has seven chapters. The first chapter, the introduction, discusses the various name changes that this condition has undergone. The second chapter discusses in detail the characteristics of children with attention deficit disorder. The third chapter discusses possible causes and the effects of the temperamental difficulties of children with attention deficit disorder on school performance, on peer relationships, on parental relationships, and on the children's feelings about themselves. The fourth chapter discusses the development of children with this disorder beginning from the preschool age range and continuing through the life span. Chapter five discusses treatment of the child with attention deficit disorder under the headings of Medical Treatment, Psychological Management, Educational Management, and Special Problems of Adolescence. The sixth chapter discusses attention deficit disorder in adults, including its clinical picture, diagnosis, and medical and psychological treatment. The last chapter, entitled "Finding Help," discusses diagnostic procedures for attention deficit disorder in general and specific difficulties in finding appropriate treatment for adult attention deficit disorder.

Like the first two editions, this book should be in the personal library of every clinician of any discipline who deals with children with attention deficit disorder, adolescents, or adults on a regular basis. The book is very clearly written and is free of technical jargon, so that it can be understood by parents and by professionals in nonmedical disciplines who might not be as familiar with medical terminology as with the terminology used in this book. This book is highly recommended for parents who have just been told that their child has attention deficit disorder. It is also highly recommended for teachers who have to deal on a daily basis with children with attention deficit disorder and who often do not have a background in recognizing and managing this disorder.

Since the first two editions of this book came on the market, two other noteworthy books written for parents have appeared that should be considered in addition to the current Wender book. These are *Attention Deficit Disorder and Hyperactivity*, 2nd ed., by Ronald J. Friedman and Guy T. Doyal (3) and *The ADD-Hyperactivity Workbook for Parents, Teachers, and Kids* by Harvey C. Parker (4). Friedman and Doyal's book is organized along lines similar to the Wender book and goes into great detail about the nature, management, and future adjustment of children with attention deficit disorder. Useful appendixes include rating scales that can be used as diagnostic instruments and a list of professional and parent organizations. *The ADD-Hyperactivity Workbook* is just what the name implies. It is a how-to-do-it manual for both parents and teachers. Charts, rating scales, examples of behavioral contracts, suggestions for teachers, reading lists for parents and teachers, and a list of parent support groups and associations are very prominent in this book.

All three of these books are recommended for parents and teachers of children with the attention deficit disorder syndrome. Although they overlap to some degree, they are dif-

ferent enough from each other that a clinician would do well to have all three in his personal library.

REFERENCES

1. Wender PH: The Hyperactive Child: A Handbook for Parents. New York, Crown, 1973
2. Wender PH, Wender EH: The Hyperactive Child and the Learning Disabled Child: A Handbook for Parents. New York, Crown, 1978
3. Friedman RJ, Doyal GT: Attention Deficit Disorder and Hyperactivity, 2nd ed. Dainville, Ill, Interstate Printers and Publishers, 1987
4. Parker HC: The ADD-Hyperactivity Workbook for Parents, Teachers, and Kids. Plantation, Fla, Impact Publications, 1988

DENNIS P. CANTWELL, M.D.
GREGORY HANNA, M.D.
Los Angeles, Calif.

Advances and New Directions: Basic Handbook of Child Psychiatry, vol. 5, edited by Justin D. Call, Richard L. Cohen, Saul I. Harrison, Irving N. Berlin, and Lawrence A. Stone; Joseph D. Noshpitz, editor-in-chief. New York, Basic Books, 1987, 720 pp., \$65.00.

Guided by a group of distinguished scholars in child and adolescent psychiatry, the publication of this volume of the *Basic Handbook of Child Psychiatry* canonizes the changes in child and adolescent psychiatry that have been apparent to many of us for a number of years. The field of child and adolescent psychiatry is developing at an ever-quickening pace; each year the number of articles and books published in this field increases. However, this increase in production only begins to reflect the substantial changes that are occurring in child and adolescent psychiatry. Dr. Noshpitz observes that several major conceptual shifts are occurring that have an impact on the field. First, there is a shift from "the classical position . . . favoring the dynamics of a case" to basing clinical reports on "survey findings . . . and the data from multiple cases." Second, standardized techniques for the assessment and categorization of childhood disorders are being developed. Third, new diagnostic and therapeutic strategies result from the application of behavioral methods, operant conditioning, and social learning theory. Fourth, the importance of understanding brain physiology and psychopharmacology as they relate to childhood disorders is being recognized. These observations herald the arrival of a new vision of what child and adolescent psychiatry is and will become.

In this volume we find an attempt not only to report advances in the field but to add to the sizable foundation offered in the first four volumes. Paralleling the first four volumes, the book's 76 chapters are organized into seven sections. Adding continuity to the handbook, the editors of the seven sections of this volume have served as editors of previous volumes in the series.

In section one, Development, we find an overview of several areas that are greatly influenced during development. Particular emphasis is placed on the neurobiological development of the CNS, the influence of environmental and hormonal factors on the CNS, and the interplay of development and the administration of medications. Notable is the chapter by Coyle and Harrison, who review the development of the principal neurotransmitter systems and discuss the im-

plications of their development on the expression of childhood psychiatric disturbances. Language acquisition, gender identity, separation-individuation, and continuity and discontinuity in development are also discussed.

In section two, Varieties of Development, we find a discussion of children's responses to circumstances such as chronic illness in themselves or their siblings. There is also a discussion of the developmental impact of incest, a timely inclusion. Obvious topics that are lacking in this section are children's responses to AIDS, organ transplantation, and drug abuse. Given the inclusiveness of the topics covered in this and previous volumes, these topics will undoubtedly appear in the next update.

Section three, Assessment, is particularly strong. Thoughtful overviews are provided of the most important issues confronting child and adolescent psychiatry—namely, assessment techniques, the use of *DSM-III-R*, and the application of biological techniques. Of particular interest are the chapters by Costello on structured interviews, Edelbrock on rating scales, and Kazdin on single-case design. Costello and Edelbrock discuss the methods by which empirical data can be collected and Kazdin demonstrates the methodology by which this information can be applied to single-case studies. Overviews of technical areas demonstrating relevance to child and adolescent psychiatry, including brain imaging techniques, assessment procedures for sleep disorders, computerized EEG, and biological tests in the diagnosis of affective disorders, balance this section and provide a glimpse of future areas of exploration.

Section four, Deviations in Development, deals with the diagnostic categories usually found in handbooks and then some. In addition to chapters written by leading authorities reviewing depression, anxiety disorders, Tourette's disorder, attention deficit disorder, psychoses, and eating disorders, there are chapters on topics that are seldom discussed but often encountered in clinical practice. These include psychic trauma, child sexual abuse, childhood narcissistic and borderline disorders, and learning disabilities. It is refreshing to see a diagnostic section that attempts to deal with the diagnostic complexity of our specialty rather than presenting a simple overview.

Section five, Therapeutics, nicely mirrors section four. Each of the diagnostic categories is covered from a therapeutic perspective. The strength of this section is the description of pharmacological, psychotherapeutic, and behavioral interventions that can be used in the management of this broad range of disturbances.

Section six, Prevention, and section seven, Impact of Current Events, round out the volume. In section six Brunstetter reviews a number of important epidemiologic investigations in child psychiatry. The remaining chapters present the results of several preventive intervention programs. The chapter by Greenspan and White is particularly interesting due to the care given to the delineation of specific issues and their operationalization for research. Section seven provides a sense of the milieu in which children live and in which the practice of child and adolescent psychiatry occurs.

It is safe to say that there is not another textbook or series of textbooks that attempts to deal with the immense scope of child and adolescent psychiatry as does the *Basic Handbook of Child Psychiatry*. Although not perfect, this volume appears to have realistic goals and an accurate view of its limitations and its audience. Rightfully, Dr. Noshpitz does not see this volume as definitive but as a temporary guidepost in the evolution of a specialty. He does not pretend to offer this as a handbook for researchers as much as a handbook for

"the mental health professional in general and the child psychiatrist in particular." Its goals are "to educate, to enrich, and to widen the perspective of practitioners, to make them aware of the newest clinical data, and to alert them to the frontiers where novel developments are likely to arise." This it does. Advanced for medical students, it provides an excellent overview for the general resident, child fellow, and clinical practitioner.

I have only three recommendations: change the title to the *Basic Handbook of Child and Adolescent Psychiatry*, include more information concerning adolescents, and publish additional updates more often. Texts such as this are needed by all subspecialties so that progress can be chronicled and so that progress can continue.

NORMAN E. ALESSI, M.D.
Ann Arbor, Mich.

Children and Criminality: The Child as Victim and Perpetrator. Contributions in Criminology and Penology 13, by Ronald Barri Flowers. Westport, Conn., Greenwood Press, 1986, 223 pp., \$35.00.

This book is devoted to sounding an alarm about dangers to and from children everywhere in the United States. It makes no effort toward a balanced consideration of these dangers; that is not the author's intent. The book is about evenly divided between the first section, *The Child as a Victim*, and the second section, *The Child as Perpetrator*.

Part one is concerned with all forms of child abuse, from infanticide to mutilation (circumcision, including circumcision of girls in some Moslem countries) to incest. Changes in moral views over time are registered. Aristotle is cited as saying, "The justice of a master or a father is a different thing from that of a citizen. For a son or slave is property and there can be no injustice to one's own property." The author emphasizes the massiveness of the problem of child abuse and the difficulties of definition of what precisely constitutes victimization. The tendency of the author is to resolve borderline cases as instances of victimization. He makes the book readable with short chapters addressing particular aspects of child victimization.

There is much evidence that child abuse is grossly underreported. The rates are increasing, but this is probably due to better reporting. Physical abuse is most likely in the very young, and the first year of life is the year of highest risk. The author points out that a strong correlation has been shown between child abuse and an unwanted pregnancy and that pregnancy soon after the birth of a previous child increases the risk of child abuse. Child abuse is more frequent in large families than in small families.

Sexual abuse is the most frequent form of child abuse (p. 76). It looms highest in the 12-17-year age range. Female victims outnumber male victims 10 to 1. The offenders are male in 97% of the cases, and the median recorded age of offenders is 31.

The second half of the book is concerned with the child as perpetrator of criminality. Various theories of delinquency are considered, essentially with the conclusion that delinquent behavior is too diverse to be accounted for under any one theory. Poor parenting and parental inconsistency are recognized as factors in the development of delinquency. The importance of cultural traditions is suggested by the fact that American children of Chinese, Japanese, and Jewish backgrounds have extremely low delinquency rates.

In an appendix the author presents a model statute for the study of child victimization and provision of treatment for the child victim. This would be a national study, set up by the Secretary of Health and Human Services, with an initial appropriation of 20 million dollars for the first fiscal year of the study.

The book is useful as a catalog of the extent and extreme variety of problems of child abuse and their overlap with the criminal behavior of children.

RICHARD L. JENKINS, M.D.
Iowa City, Iowa

Hyperactive Children Grown Up: Empirical Findings and Theoretical Considerations, by Gabrielle Weiss and Lily Trokenberg Hechtman. New York, Guilford Press, 1986, 352 pp., \$32.50.

Despite decades of research, several changes in name, and the medication of thousands of children, the syndrome of hyperactivity remains, for many, a controversial construct, still capable of generating scholarly debate and legal dispute. This entity, once called "minimal brain dysfunction" and now termed "attention-deficit hyperactivity disorder" (DSM-III-R), is among the most often diagnosed in child psychiatry in the United States but is rarely noted in Great Britain. Given this controversy, the title chosen by Weiss and Hechtman, implying as it does the existence of a definite syndrome of related behaviors and characteristics with clear implications for the future of the affected child, suggests a statement of faith. Indeed, the core of the book is the authors' own ongoing study of children they have been following for more than 15 years. The final chapter is devoted to a personal recollection of one of their subjects. How could they not believe in the validity of the syndrome to which they have devoted much of their lives? Nevertheless, this book is, by and large, a thoroughly annotated, research-oriented text that begins with an overview chapter including a section entitled *Does the Hyperactive Syndrome Exist?* Clearly, Weiss and Hechtman want to appeal to both our hearts and our minds.

The organization of the book, as determined by section and chapter headings, seems superficially clear enough. The six major parts of the book include an overview, a discussion of the syndrome from a developmental viewpoint, a large collection of chapters on various characteristics of the hyperactive syndrome in adulthood, a group of three chapters on potentially predictive factors, two chapters on treatment issues, and a concluding section on the recollections of adult hyperactive subjects. In the preface, the authors indicate their desire to "fill the interstitial spaces between empirical findings of many investigators and of our own studies" with psychiatric "impressions" (p. x). To do so, they have chosen a topical approach in which "each chapter is written in such a way as to provide the reader with a review of the particular area, its controversial issues, available data relating to these diverse views, possible conclusions, and . . . directions for future interventions and research" (p. x).

Although the organizational intent is clear, the effect will be confusing, at least for some readers. Each chapter is intended to function almost as a freestanding paper. Generally, a review of several studies culminates in a discussion of findings from the authors' own follow-up study. The problem with this approach is that anyone who does not use the book as a set of independent reviews but, instead, attempts to read

it straight through encounters the same studies over and over, each time from a slightly different vantage point. Inevitably, there is also redundancy in the authors' discussion of these papers and of their own work, only partially relieved by cross referencing to previous or subsequent chapters. To avoid confusion while reading a given chapter it is necessary to clear one's mind of previous chapters to a large degree. This particular déjà vu aspect of the text makes it difficult to gain an overall view of the literature. Moreover, the first chapter is poorly edited, with several instances of awkward sentence construction and otherwise difficult grammar.

There are, of course, weaknesses in the authors' study, just as there are in the studies they review. Following any group of individuals over several years in a scientifically rigorous fashion is a Herculean task. Inevitably, more and more individuals are lost to follow-up. Almost as certainly, the researchers discover things they wish they had done differently or, at least, not left out. Weiss and Hechtman's study is no exception. The original group of 104 children with hyperactivity had dwindled to 76 at the end of 10 years. The control group was belatedly added at the 5- and 10-year follow-ups.

The authors have done their best to make allowances for these deviations from the ideal and are careful to include data, when available, on the differences between individuals lost to follow-up and individuals remaining in the study. They also indicate which outcome ratings were and which were not made blind to diagnosis (probably an unavoidable problem when a small group of researchers follows a shrinking number of children over several years). It seems clear that Weiss and Hechtman are aware of the limitations of their study and are presenting it fairly. One can conclude from this presentation that the greatest limitations stem from two aspects of the study design: first, the comparison group, although well controlled on several variables, is a "normal" rather than a "clinic-referred" sample; second, the assignment of treatment received was naturalistic rather than random.

The consequence of using a normal control group is that there must always be a lingering doubt as to whether significant differences between groups should be attributed to the specific syndrome of hyperactivity, as they are by the authors, or to the nonspecific behavioral, emotional, and family variables that cause a child to be referred to a psychiatric clinic. This is especially true because children in the control group, even though matched in age with hyperactive children, were not chosen until 5 to 10 years after the hyperactive children were chosen. Since control children had to have been free of behavior problems and to have never failed a grade in school before being recruited and children in the hyperactive group who were lost to follow-up over the years tended to be those with poorer outcomes, the differences between hyperactive and control children are likely to be considerably exaggerated relative to what they might have been if all subjects had been chosen at the same time.

Comparison between different treatment groups in this naturalistic design must be suspect because treatments were not randomly assigned and the groups may differ in other known or unknown ways that could affect outcome. Weiss and Hechtman allude to this difficulty in justifying their comparison of the adult outcome of hyperactive children who received no stimulants during childhood with the adult outcome of those who did. They suggest that the former group differ from the latter only in the fact that they were seen in the years before stimulants were generally prescribed. In other words, the children in the two groups received differing treatments only because prevailing medical practice had changed.

Although this is a simplification, it is a line of reasoning that has been accepted elsewhere in psychiatric research.

Despite these criticisms, I think that Weiss and Hechtman have performed a great service by collecting a large body of research on the long-term outcome of hyperactivity to supplement their own study. They use this body of research to address several issues central to understanding implications of the syndrome we now call attention-deficit hyperactivity disorder, such as the nature of the relationship between hyperactivity and adult antisocial behavior, whether hyperactivity predisposes to substance abuse, the role of pharmacological treatments, and, of course, whether and in what way the syndrome of hyperactivity persists directly into adulthood.

Even taking into account my reservations about the methodology, I think that many of the conclusions reached are persuasive. Given the nature of their control group it can be argued that Weiss and Hechtman's findings are most convincing when they indicate little or no significant difference between hyperactive and control subjects. For example, despite some literature to the contrary, they found no evidence of a higher rate of psychosis in their hyperactive group. Also contradicting some fairly common views in the literature, although requiring somewhat more complicated analysis, the rate of alcohol use in the adult hyperactive subjects appeared not to be much higher than the rate among the control subjects. Moreover, even positive findings in the sense of clear differences between the two groups in the rate of specific symptoms are difficult to dismiss when the symptoms are consistently seen at 5-, 10-, and 15-year follow-ups. Whether it is the syndrome of hyperactivity that is responsible or some other unidentified factor or factors, it seems clear that the two groups differ in a fashion that persists despite a variety of changes over several years in individual levels of maturity and life circumstances.

Unquestionably, then, this book has much to reward the careful reader. Like Lee Robins's now classic work, *Deviant Children Grown Up* (1), which, given the similarity in title and concept, may very well have been an inspiration for Weiss and Hechtman, *Hyperactive Children Grown Up* is a candidate to become a standard in the field. If it succeeds it will be on the strength of the wealth of detail provided about the lives of young people who have been given the diagnosis of hyperactivity. It is a book that both convinces us of the need for more and better research and reminds us in direct, personal terms that the abstract syndrome sometimes obscures the very real needs of the hyperactive child.

REFERENCE

1. Robins LN: *Deviant Children Grown Up* (1966). Huntington, NY, Robert E Krieger, 1974

JAMES BEEGLY, M.D.
Iowa City, Iowa

FAMILIES AND FAMILY THERAPY

The State of the Art in Family Therapy Research: Controversies and Recommendations, edited by Lyman C. Wynne. New York, Family Process Press, 1988, 291 pp., \$18.00 (paper).

This book is an excellent collection of papers on the current state of research in family therapy and what directions it

should now take. Originally given at a conference jointly sponsored by the National Institute of Mental Health and the Board of Directors of *Family Process*, the papers are authored by outstanding investigators of family therapy who discuss key conceptual issues, the selection of variables, the design of outcome studies, approaches to the study of process, and methods of data analysis.

Those who do research will find that this book contains much that will be useful as well as much that is familiar. No one should undertake research on family therapy without reading it. However, it contains no surprises. The issues discussed by these experienced investigators of family therapy are similar to those which have arisen in psychotherapy research of individuals and groups. Some of the major issues that particularly troubled the conference participants were the following: 1) Should we study outcome to prove to funding agencies that family therapy is on the right track and therefore deserves fees for service? 2) Should we study process to learn what makes a difference in outcome with which clients? This would be more useful to therapists. 3) How do we find the optimism to undertake a large and complicated study that must have enough of the right kind of patients, the appropriate ways to decide what kind they are and are not, and the instruments suitable for assessing the processes leading to change and the kinds of changes which occur? 4) Finally, how do we find a way to fund the study, all the while supporting ourselves in a suitable place to live and work. One hopes that investigators will find this book a progress report rather than a eulogy.

For the clinician, the book is not nearly so useful. Unfortunately, as is true of individual psychotherapy research, family therapy research has had comparatively little impact on clinicians. One obvious reason is that outcome studies are comforting to family therapists regardless of their theoretical orientation because conjoint treatment of couples is superior to individual treatment of problem marriages and behavioral and psychodynamic therapies appear to have essentially similar improvement rates.

There are other reasons, however, why family therapy research has had less impact than it might on clinical practice. First, as many of the authors in this book indicate, researchers and research tend to go where there are both money and method. As Stanton says, look where there is light rather than in the shadows to find what is lost. Hence, as might be expected, Epstein believes that funding should follow theoretical clarity, specificity of intervention, and therapists who follow guidelines set out in manuals. Much may be learned in this way, but in all probability there will be no surprises. The only way out of this predicament will be for people who approach family problems very differently to begin to do research; these investigations will probably not be funded because they are nonestablishment. Auerswald's discussion of the ecosystems paradigm is an example of such an approach, but he is a rare representative of this viewpoint in that he has actually attempted to carry out research. The book, while fulfilling its title in describing the state of the art in family therapy research, does not break new ground.

The second major reason why there are no surprises is that research methods are not well suited to investigate therapies whose goals are to foster action based on understanding. Most clinicians know that couples and families come for therapy either with a story whose ending they seek to change or with a problem person whom they seek to change. The first group of families represent the everyday problems of relationships—couples who do not get along and children who do poorly in school and/or do not mind their parents.

Those who face the second type of problem call this first group the "worried well," but we all know how unhappy a sour marriage can be and we have seen parental despair over a troubled child. Yet there can be little question that the second type of situation, that of a couple or family with a problem person, is different. The problem person may be alcoholic, schizophrenic, depressed, anorexic, abused, or even abusive, and usually he or she is sent for help and their family wants to know how to help this person. The clinical dilemma is that these two groups overlap and perhaps can each lead to the other. There are theories taking strong positions on this dilemma (biological, individual, and familial), and there are true believers. These theories foster clinical confidence but unfortunately are based on too little information about either etiology or intervention.

All this is well-known, so what is the point? It is that research on how to intervene successfully with certain kinds of problems can lead and has led to useful information. There are specific interventions suitable for specific entities, such as psychoeducational groups for families of schizophrenic patients and parental behavioral methods for use with delinquent boys as described by Patterson and Chamberlain. Unfortunately for investigators working within the standard paradigm and using usual research methods, interventions in the stories of individuals are different in quality than these rather specific interventions. How can we study when to do an interview with the family of origin and whether "creative separations" work when the goal of these interventions are improved relationships with parents and spouse rather than alleviation of symptoms? Research on family therapy would be more valuable and more influential if these two types of marital and familial problems were not confounded. Positivist methods of study are poorly suited to help us understand how people can lead more meaningful and satisfying lives. It is here that practical wisdom in the sense that Aristotle described it is vital—"how to live well and do well."

HENRY GRUNEBaum, M.D.
Cambridge, Mass.

Children and Families: Studies in Prevention and Intervention, edited by Euthymia D. Hibbs. Madison, Conn., International Universities Press, 1988, 341 pp., \$65.00.

As I read this work, I thought of Margaret Ribble's 1943 book entitled *The Rights of Infants* (1). She discussed physical and emotional requirements for infant survival and development based on her observations and made conclusions influenced by her training in pediatrics, psychiatry, and psychoanalysis. She did not present data other than her own observations to support her conclusions.

Data abound in *Children and Families*, a collection of 37 papers presented at the World Congress on Infancy as Prevention held in Athens, Greece, in the summer of 1984. The chapters are arranged in sections on Prevention, Intervention, Parent-Infant Interaction, Cognition and Education, Health and Behavior, Day Care, The Impaired Child, Adoption, and The Family. Their content varies from statements of opinion to reports of controlled research with reviews of the related literature, but they all deal with the rights and needs of infants to develop physically, emotionally, and cognitively. There are 72 contributors from eight countries. They acknowledge the work of Freud, Bowlby, Erikson, Mahler, and Piaget, but no one mentions Winnicott—or Rib-

ble. Most of the contributions, which range in their order of abstraction from the current recommendations on vaccination to factors that facilitate cognitive development, are focused on the importance of the parent-child relationship and opportunities to improve the child's early environment. There are reports on experimental projects to provide early preventive and remedial nursing services to disadvantaged infants. There is a discussion of the "politics of contraception" and one on the use of waterbeds in place of conventional incubators for children born prematurely to prevent the motor, cognitive, and emotional deficits associated with premature birth. A chapter on maternal-infant bonding includes criticism of the "medicalization of childbirth in the twentieth century." Another reports on studies of how early vocal and social interaction between mother and infant affects cognitive development. A chapter summarizes the findings from a dozen longitudinal studies of infant education with disadvantaged children.

Larry B. Silver discusses difficulties that may occur between infant and mother because of the persistence of certain reflexes, such as the tonic neck reflex, which normally are not present after the first 6 months of life. He also points out that some infants are hypersensitive to touch because of a slow-to-mature nervous system.

In Nurnberger and Gershon's chapter on genetic factors and genetic counseling, the information on genetic factors in mood disorders is so condensed as to be nearly opaque, but the brief section on counseling is a model of clarity and includes the following tips: The major psychiatric disorders appear to be inherited, but the mode of transmission is not known. Biological markers are not yet clinically useful, but available empirical risk estimates are useful in genetic counseling. "A request for genetic counseling should be approached as a problem in short-term psychotherapy" (p. 430). Nurnberger and Gershon also discuss the evidence (very meager) for a viral etiology of schizophrenia (p. 432) and for the possibility that drug abuse precipitates persisting mental disorders in patients who are not otherwise predisposed (p. 434).

In addition to the primary focus of the book, namely, prevention through early intervention, this material is of interest to all psychiatrists because of its implications for the epidemiology of the disorders we treat. Specifically, Hibbs and Sansbury report on their research on "The Impact of the Quality of Family and Peer Relations on Adolescent Pregnancy." This was a controlled study using questionnaires and structured interviews. Many of their findings contradict conventional thinking about pregnant teenage girls, such as the belief that their object relations are immature and their relationships with their mothers are angrily dependent. Such findings appear to illustrate what Michael Rutter (2) has called the developmental perspective in epidemiologic research: sexual activity and contraceptive carelessness may be appropriate to the youngster's stage of development rather than evidence of psychopathology.

REFERENCES

1. Ribble MA: *The Rights of Infants*. New York, Columbia University Press, 1943
2. Rutter M: Epidemiological approaches to developmental psychopathology. *Arch Gen Psychiatry* 1988; 45:486-495

WILLIAM R. FLYNN, M.D.
Napa, Calif.

ANXIETY DISORDER

Anxiety and Stress Disorders: Cognitive-Behavioral Assessment and Treatment, edited by Larry Michelson and L. Michael Ascher. New York, Guilford Press, 1987, 624 pp., \$39.50.

This book is one example of the trend to apply the advances made in cognitive-behavioral therapy of depression to a variety of anxiety disorders. This edited volume contains 21 chapters divided into two sections. The first section of five chapters focuses on theoretical foundations, assessment methods, and overviews of treatment approaches, and the second section contains 16 chapters addressing applications to clinical situations. Single chapters cover all the *DSM-III-R* anxiety disorders, including simple phobia, social phobia, generalized anxiety, agoraphobia, panic disorder, posttraumatic stress disorder, and obsessive-compulsive disorder. Additional chapters also cover anxiety difficulties in special clinical populations, including children, the mentally retarded, and the elderly. Nonpsychiatric conditions amenable to cognitive-behavioral therapy receive attention in chapters on headaches, essential hypertension, and anxiety related to chemotherapy and other medical procedures.

The methodological section is highlighted by an excellent chapter reviewing the multitude of already completed trials of cognitive-behavioral therapy for anxiety. This chapter, written by Lars-Goran Ost and Lars Jansson, tabulates more than 100 outcome studies of cognitive-behavioral therapy in various anxiety disorders. Important methodological problems, such as recruitment methods, inclusion criteria, intervention specificity, study design, measurements, and outcome criteria, are highlighted. Knowledge of these completed studies is pertinent to understanding the importance of designing future cognitive-behavioral therapy outcome studies.

The clinical application chapters in this volume are of variable quality; some have more clinical utility than others. Excellent chapters include those addressing agoraphobia, social phobia, obsessive-compulsive disorder, and hypertension. Here the reader will find well-referenced summaries of current experience of cognitive-behavioral therapy in these specific disorders. The practical clinical implementation of cognitive-behavioral therapy for specific disorders is addressed in most of the chapters covering specific anxiety diagnoses.

This volume is a necessary reference for researchers doing cognitive-behavioral therapy outcome studies. Clinicians using cognitive-behavioral therapy in daily practice with patients with anxiety disorders will also find the volume quite helpful. This book does not substitute for more technique-oriented standard references of cognitive-behavioral therapy, such as those by Beck and Emery (1) or Wolpe (2), but the editors provide a state-of-the-art review, and the individual authors provide guidance for designing important and methodologically sound future studies to aid in the treatment of patients with anxiety disorders.

REFERENCES

1. Beck AT, Emery G: *Cognitive Therapy of Anxiety and Phobic Disorders*. New York, Basic Books, 1985

2. Wolpe J: The Practice of Behavior Therapy, 3rd ed. New York, Pergamon Press, 1983

WILLIAM R. YATES, M.D.
Iowa City, Iowa

Post-Traumatic Stress Disorder: Diagnosis, Treatment, and Legal Issues, 2nd ed., by C.B. Scignar, M.D. New Orleans, Bruno Press, 1988, 330 pp., \$49.95; \$32.95 (paper).

Compared with Dr. Scignar's first edition of this book, published in 1984, the second edition has more chapters, has more pages of text, and is 52% more expensive in the hardcover version. Except for the chapter on "Invisible Trauma and PTSD: Toxic Substances, Radioactivity, and Pathogenic Microorganisms," the other new chapters are essentially expansions of chapter sections from the first edition. This chapter does, however, introduce a subject that will almost certainly receive a great deal of clinical and forensic attention in the future, given such disasters as the chemical plant explosion in Bhopal, India, the carcinogenic effect of toxic substances in the Love Canal, the Three Mile Island and Chernobyl nuclear plant disasters, and the AIDS crisis.

The most outstanding features of Dr. Scignar's second edition are the rewriting of major portions of the text for improved clarity and the updating of the reference list to include relevant literature published since the first edition appeared. The second edition retains the essence of the first edition and gives the practicing clinician a fundamental approach to understanding, treating, and forensically assessing individuals with posttraumatic stress disorder (PTSD).

Throughout the book, Dr. Scignar conceptualizes PTSD by using a biopsychosocial-like model containing the "three Es" and the "spiral effect." The three Es stand for environment, encephalic events, and endogenous events. Dr. Scignar explains the etiology of PTSD in terms of the interplay of the three Es. The spiral effect refers to a cyclotron-like process involving the three Es that leads to maintenance and/or worsening of PTSD symptoms. With this model, PTSD can easily be explained to patients. Further, its uncomplicated nature can facilitate effective communication when presenting PTSD to attorneys, judges, and juries. For treatment of PTSD, Dr. Scignar describes in sufficient detail a cognitive-behavioral approach that is likely to be clinically useful for the practitioner.

Unfortunately, no single work on PTSD can expect to cover the vast fund of knowledge available on the disorder. For example, Dr. Scignar's book only briefly mentions the neurobiological aspects on both research and clinical levels. Nevertheless, the book appears to be well suited for the general psychiatric practitioner who wants exposure to an easily understandable text about the clinical aspects of PTSD. The forensic material in Dr. Scignar's book can capture the interest of forensic psychiatrists but seems to best serve as an illustrative introduction for most readers. Thus, a shortcoming of Dr. Scignar's book appears to be underemphasizing the need for adequate forensic training before participating in the legal area.

Overall, *Post-Traumatic Stress Disorder* is a worthwhile addition to the library of clinical psychiatrists who evaluate and treat patients with PTSD.

GREGORY B. LEONG, M.D.
Los Angeles, Calif.

Reprints of Book Forum reviews are not available.

Letters to the Editor

Quinine for Neuroleptic-Induced Dystonia and Muscle Stiffness

SIR: Anticholinergic medications, prescribed to treat side effects of neuroleptics, produce unpleasant side effects themselves, are not always effective, and have the potential for abuse. To my knowledge, there have been no reports on the use of quinine as a supplement or an alternative for the treatment of dystonias and muscle stiffness induced by neuroleptics. This traditional drug for treatment of malaria is also a recognized treatment for nocturnal leg cramps.

Mr. A, a 24-year-old white man being treated with 15 mg/day of haloperidol for a psychosis not otherwise specified, complained of muscle cramps and stiffness, which had not been present before neuroleptic treatment. Benzotropine mesylate, 2 mg t.i.d., helped somewhat but caused an unpleasant dry mouth. Previous trials of amantadine, procyclidine, and trihexyphenidyl at maximum recommended doses had been less successful.

Mr. A was simultaneously being treated with desipramine, 150 mg b.i.d., for recurrent depression; verapamil, 80 mg t.i.d., for prophylaxis of migraine; and 50 mg/day of triamterene and 25 mg/day of hydrochlorothiazide for essential hypertension.

On his internist's advice, Mr. A began drinking two quarts per day of tonic water, which contains 152 mg of quinine per quart. Within 3 days his symptoms had disappeared. On two subsequent occasions when he ran out of tonic water, the symptoms reappeared, but they were relieved when he resumed drinking tonic water. While he was drinking tonic water, his consumption of other fluids decreased, so that his daily fluid intake remained constant. At no time were there any signs or symptoms of cinchonism.

Quinine, aside from its antimalarial properties, has several effects on skeletal muscle. It reduces responses to acetylcholine at the motor end plate, increases the period of refractoriness to stimulation, and causes a redistribution of calcium in muscle fibers (1). These are the postulated reasons for its effectiveness in nocturnal leg cramps, although controlled studies only weakly support its efficacy (2). The two major drawbacks to the use of quinine are occasional hypersensitivity and dose-related cinchonism, even at doses as low as 300 mg/day. Nonetheless, it may be useful to systematically study the use of quinine for neuroleptic-induced dystonias and muscle stiffness because of its possible efficacy, relative safety, acceptability to patients, and minimal potential for abuse.

REFERENCES

1. Gilman AG, Goodman LS, Rall TW, et al (eds): Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 7th ed. New York, Macmillan, 1985, p 1043

2. Warburton A, Royston JP, O'Neill CJA, et al: A quinine a day keeps the leg cramps away? *Br J Clin Pharmacol* 1987; 23:459-465

LEONARD LEVEN, M.D.
New York, N.Y.

Panic Attacks Triggered by Photic Stimulation

SIR: The recent articles "Patients With Panic Attacks and Abnormal EEG Results" (1) and "Lack of Efficacy of Carbamazepine in the Treatment of Panic Disorder" (2) discussed the controversy about the epileptiform etiology of panic disorder. Photic stimulation is commonly used in EEG investigations. Certain reactions to photic stimulation are suggestive of neurological problems. For example, a prolonged photoconvulsive response is highly suggestive of epilepsy (3). Conceivably, the finding that panic attacks are triggered by photic stimulation may further support an epileptiform hypothesis. To my knowledge, there are no such findings in the literature; thus, I wish to describe the first reported case of panic attacks precipitated by photic stimulation.

Ms. A, a 39-year-old woman, had a 5-year history of panic disorder. The panic attacks were characterized by shortness of breath, palpitations, tingling sensations, chest pain, and fear of dying. The attacks would occur at a frequency of up to three per day. The attacks were not related to any particular environmental stimuli. She subsequently developed some mild agoraphobic and hypochondriacal symptoms. Cocaine use increased the frequency and intensity of the attacks. There was no history of head injury, epilepsy, or other neurological disorder. There was no family history of panic or epileptic disorder.

Ms. A was initially referred to a neurologist. The results of a neurological examination, a CT scan, and two EEGs were all within normal limits. However, in both EEGs, during photic stimulation, she developed full-blown panic attacks. She was unwilling to have further specialized EEG studies for fear of bringing about another panic attack. On another occasion she had a panic attack at work when a fluorescent light began flickering. She was subsequently seen at an outpatient psychiatry clinic, where panic disorder was diagnosed.

Ms. A was initially treated with imipramine, up to 200 mg/day. This regimen resulted in partial improvement. She refused to increase the imipramine dose because of an unfounded fear of long-term side effects. Therefore alprazolam, up to 1 mg t.i.d., was added. The alprazolam resulted in further, but still incomplete, recovery. The alprazolam was gradually withdrawn and clonazepam, 0.5 mg t.i.d., was instituted. This low dose of clonazepam led to such a degree of improvement that the imipramine was discontinued without a significant recurrence of panic attacks.

Although this is the first reported case of photic stimulation inducing a panic attack, Niedermeyer et al. (4) stated that patients with hysterical reactions and anxiety states had a relatively high incidence of photoconvulsive responses to photic stimulation. Unfortunately, at the time of this observation, *DSM-III* criteria were not available for use in determining whether this photoconvulsive response was specifically related to panic disorder.

This patient showed a remarkable response to an anticonvulsant, clonazepam, while demonstrating only a mild response to other antipanic agents. Her response is indirectly suggestive of epileptiform phenomena.

Further research into photic stimulation and panic disorder may be warranted in efforts to delineate the etiology of the disorder and, possibly, to define treatment-responsive subgroups of patients with the disorder.

REFERENCES

1. Edlund MJ, Swann AC, Clothier J: Patients with panic attacks and abnormal EEG results. *Am J Psychiatry* 1987; 144:508-509
2. Uhde TW, Stein MB, Post RM: Lack of efficacy of carbamazepine in the treatment of panic disorder. *Am J Psychiatry* 1988; 145:1104-1109
3. Reilly EW, Peters JF: Relationship of some varieties of electroencephalographic photosensitivity to clinical convulsive disorders. *Neurology* 1973; 23:1040-1057
4. Niedermeyer E, Fineyre F, Riley T, et al: Myoclonus and the electroencephalogram: a review. *Clin Electroencephalogr* 1979; 10:75-95

H. ROSENBLAT, M.D., F.R.C.P.(C)
Toronto, Ont., Canada

Tardive Dyskinesia With Complaints of Pain

SIR: Tardive dyskinesia does not usually present as a painful disorder (1). However, the dental literature contains two cases of tardive dyskinesia associated with pain due to "trauma between mucosa and dentures" (2). I wish to report on a patient with probable tardive dyskinesia who presented with complaints of pain.

Ms. A, a 79-year-old woman with recurrent major depression, had been treated in the past with ECT, antidepressants, and neuroleptics. She was doing poorly on a regimen of clonazepam and perphenazine, so these were gradually withdrawn. Two weeks after discontinuation of the perphenazine, she began to complain that her tongue "hurt all over." Examination showed a prominent lingual dyskinesia with lip puckering and a lingual traumatic ulcer. The patient was unaware of any oral movements. Viscous lidocaine 2% and glyoxide failed to alleviate the pain, which persisted for 5 weeks. Reintroduction of perphenazine, 4 mg/day, largely suppressed the dyskinesia after 6 days, with coincident disappearance of the pain.

To establish a connection between the dyskinesia and the pain, the perphenazine was discontinued on two more occasions. Each time the pain and an exacerbation of the dyskinesia recurred within 2 weeks. Both then abated within a week of reinstitution of perphenazine. These two episodes were not accompanied by tongue lesions.

The relief obtained by this patient with the restarting of perphenazine was dramatic. Since other remedies, such as

viscous lidocaine and glyoxide, had been given to her with great expectations, it seems unlikely that her response to perphenazine was a placebo response.

A concern was that the pain was secondary to traumatic tongue lesions incurred as the tongue moved against the teeth. I do not believe this to be the case, however, because the last two episodes were unaccompanied by lingual lesions, and one would expect oral lidocaine to relieve pain due to lingual ulcerations to some degree. It did not.

There are many reported causes of oral dyskinesias, and it is impossible to be absolutely certain this patient had tardive dyskinesia (3). Factors such as her age at onset, the lack of progression over 2 years, and the lack of upper facial involvement argue against other extrapyramidal disorders such as Wilson's disease, Huntington's disease, and Meige's syndrome. She was not taking dopamine agonists, anticonvulsants, or anticholinergics. She did not wear dentures. Results of thyroid and liver studies, calcium and phosphorus levels, and a CBC were all normal. Spontaneous idiopathic dyskinesias have been reported in the elderly (4), but it is not clear whether neuroleptics suppress such dyskinesias. Although a spontaneous dyskinesia was reported to have been suppressed by clonidine plus levomepromazine (5), it is unclear whether the clonidine or the neuroleptic was responsible for the improvement in that case. Because spontaneous dyskinesias may appear similar to oral tardive dyskinesia (4), it may be impossible to differentiate tardive dyskinesia from spontaneous dyskinesia in elderly neuroleptic-exposed individuals. In this case, because of the patient's history of exposure to neuroleptics, my colleagues and I are inclined to think that she had tardive dyskinesia. It is a moot point. Either way, we believe that the painful presentation is noteworthy.

There has been growing recognition of the varying manifestations and complications of tardive dyskinesia. This report is to alert clinicians that lingual dyskinesias may present with complaints of tongue pain.

REFERENCES

1. Baldessarini RJ: Clinical and epidemiologic aspects of tardive dyskinesia. *J Clin Psychiatry* 1985; 46(4, section 2):8-13
2. Bassett A, Remick RA, Blasberg B: Tardive dyskinesia: an unrecognized cause of orofacial pain. *Oral Surg Oral Med Oral Pathol* 1986; 61:570-572
3. Granacher RP Jr: Differential diagnosis of tardive dyskinesia: an overview. *Am J Psychiatry* 1981; 138:1288-1297
4. Blowers AJ, Borison RL: Dyskinesias in the geriatric population. *Brain Res Bull* 1983; 11:175-178
5. Nishikawa T, Tanaka M, Tsuda A, et al: Clonidine therapy for tardive dyskinesia and related syndromes. *Clin Neuropharmacol* 1984; 7:239-245

ROBERT W. HIERHOLZER, M.D.
Perry Point, Md.

Doxepin for Treatment of Mania

SIR: Recently there has been much controversy in the literature regarding the ability of antidepressants to induce mania (1, 2). I should like to present the case of a patient whom I treated for mania with only an antidepressant.

Ms. A, a 60-year-old woman, had a long history of bipolar disorder, mixed, with psychotic features. She had been under psychiatric care for about 15 years—since her first hospitalization for "depression." Her father and

brother had also been diagnosed as having bipolar disorder. Since her first hospitalization she had shown the classic symptoms of a bipolar patient. Her manic periods were marked by auditory hallucinations, pressured speech, irritability, lability of mood, increased spending of money, increased appetite, decreased sleep with complete insomnia for 3-day periods, the beginning of many tasks simultaneously with inability to complete them, poor concentration, and decreased attention. She had had a trial of lithium at therapeutic serum levels (up to 1.4 meq/liter) with no effect. She insisted that the only medication which had helped her was doxepin at a dose of 100–150 mg h.s.

Over the last year Ms. A presented on three occasions with her "usual" manic symptoms. Each time, doxepin alone was successful in lowering her affective state to the point of euthymia. Cessation of the drug resulted in elevated mood within 10 days. Restarting the antidepressant resulted in euthymia and resolution of the psychosis within 14 days.

I have no explanation for this seemingly paradoxical effect in this patient. Nonetheless, I have every intention of continuing her maintenance treatment of doxepin, 100 mg h.s. by mouth.

REFERENCES

1. Wehr TA, Goodwin FK: Can antidepressants cause mania and worsen the course of affective illness? *Am J Psychiatry* 1987; 144:1403–1411
2. Lewis JL, Winokur G: The induction of mania: a natural history study with controls. *Arch Gen Psychiatry* 1982; 39:303–306

NEIL S. KAYE, M.D.
Worcester, Mass.

Lack of Effect of Naloxone on Selection of Nutrients by Bulimic Women

SIR: Several investigators have demonstrated a suppression of eating behavior associated with administration of opioid antagonists in various animal species. However, there are few data on possible changes in specific macronutrient preferences associated with the use of these compounds. In one study, rats administered naloxone consumed less fat and carbohydrate than control animals receiving saline solution (1). No influence on protein intake was observed. Fantino et al. (2) had eight normal-weight women rate the pleasurable effect of sucrose solution versus that of salt solution. The individuals taking naltrexone reported significantly less desire for sucrose than those taking placebo. Morley et al. (3) found that a bolus of 2 mg of naloxone followed by infusion of 1 mg/hour for 24 hours attenuated preference for fat and carbohydrate in two human subjects. Whether these effects would continue with chronic administration of a long-acting narcotic antagonist such as naltrexone has not, to our knowledge, been investigated.

We conducted a placebo-controlled, double-blind crossover study of naltrexone hydrochloride, an orally active opioid antagonist, in 16 normal-weight women diagnosed as having bulimia nervosa (4). The subjects kept food diaries of meals, snacks, and binge-eating episodes for 1 week at baseline, 1 of the 3 weeks during the placebo phase, and 1 of the 3 weeks during the naltrexone phase. Total kilocalories, kilocalories of individual macronutrients, and percentage of

dietary intake for each macronutrient were calculated separately for nonbinge and binge-eating periods. Data were analyzed for differences in kilocalories consumed and macronutrient choice when subjects were taking the active drug and when taking placebo. No significant differences were noted on any of these variables between periods when the subjects were taking naltrexone and periods when they were taking placebo. The drug was also ineffective in suppressing binge-eating behavior (4).

The results of our study do not suggest that narcotic antagonists have an effect on macronutrient selection in humans diagnosed as having bulimia nervosa. However, our results must be considered preliminary, given the small sample size, and should not be generalized to other populations, since the eating behavior of this group of patients is certainly atypical.

REFERENCES

1. Marks-Kaufman R, Kanarek RB: Modifications of nutrient selection induced by naloxone in rats. *Psychopharmacology* 1981; 74:321–324
2. Fantino M, Hosotte J, Apfelbaum M: An opioid antagonist, naltrexone, reduces preference for sucrose in humans. *Am J Physiol* 1986; 200:R91–R96
3. Morley JE, Levine AS, Yim GK, et al: Which opioid receptor mechanism modulates feeling? *Appetite* 1984; 61:61–68
4. Mitchell JE, Christenson G, Jennings J, et al: A placebo-controlled, double-blind crossover study of naltrexone hydrochloride in outpatients with normal weight bulimia. *J Clin Psychopharmacol* (in press)

ELIZABETH SOLL, B.S.
BRENDA THOMAS, R.D.
JAMES E. MITCHELL, M.D.
Minneapolis, Minn.
JOHN MORLEY, M.B., B.Ch.
Los Angeles, Calif.

Treatment of a Refractory Depression With a Combination of Fluoxetine and d-Amphetamine

SIR: The following is, to my knowledge, the first published report of the use of fluoxetine in combination with a psychostimulant. The patients's depression had proved refractory to imipramine with and without various augmentation therapies.

Mr. A, a 36-year-old man, sought treatment 2 months after becoming profoundly depressed. He suffered from anhedonia, loss of ambition, lack of energy, and an inability to cry or laugh. He had gained 20 pounds as a result of his markedly increased appetite despite the fact that eating now gave him no pleasure. He also complained of hypersomnia.

Mr. A failed to benefit from a trial of imipramine, 300 mg/day, that lasted more than 22 months. Imipramine was first used alone and then, with informed consent, in combination with various other medications: 6 weeks of imipramine alone at 300 mg/day; then imipramine combined with 40 µg/day of triiodothyronine for another 2 weeks; followed by a combination of imipramine and methylphenidate, 20 mg/day, for 5 weeks; then imipramine with tryptophan, 8000 mg/day, for 2 weeks; and, finally, imipramine with L-thyroxine, 0.15 mg/day, for an additional 2 weeks.

Throughout all of these trials, Mr. A remained thoroughly joyless. Furthermore, he would not agree to a trial of either lithium or a monoamine oxidase inhibitor or to an increase of imipramine above 300 mg/day. He also refused referral for ECT. Finally, imipramine, still at 300 mg/day, was augmented for a period of 8 months with *d*-amphetamine, raised ultimately to 45 mg t.i.d. The patient's interest in maintaining *d*-amphetamine was encouraged by the fact that, when taking this drug, he was able to obtain erections. (Nevertheless, his libido remained markedly diminished, and his wife, not he, made occasional sexual overtures.) Finally, *d*-amphetamine, too, was abandoned.

Imipramine was discontinued when fluoxetine became available. Five months later, Mr. A's depression was still unchanged, and *d*-amphetamine was added to the 60 mg/day of fluoxetine. He experienced modest benefit while the dose of *d*-amphetamine was being titrated. A dose of 45 mg t.i.d. of *d*-amphetamine (the same dose used unsuccessfully during the trial with imipramine) combined with fluoxetine, 60 mg/day, resulted in a significant and sustained clinical improvement.

The patient, for the first time in 2½ years, found relief from depression. His libido, energy, and ambition returned. He also lost 10 pounds while maintaining a good appetite. Over the next 5 months, he did not develop tolerance to the antidepressant effects of this combination.

The dose of 45 mg t.i.d. of *d*-amphetamine is well in excess of conventional doses (1, 2). Fluoxetine was therefore briefly increased to 80 mg/day in an effort to obtain an antidepressant effect sufficient to permit discontinuation of the *d*-amphetamine. However, even with the higher dose of fluoxetine, Mr. A relapsed on each of four subsequent occasions when *d*-amphetamine was not used.

Reimherr et al. (3) reported that in patients whose depressions were characterized by chronicity, previous poor response to antidepressants, and atypical features (hyperphagia and hypersomnia), fluoxetine was more effective than imipramine. In the case of Mr. A, fluoxetine was ineffective until *d*-amphetamine was added. Thus, the role of *d*-amphetamine seems vital, as does the role of fluoxetine, since neither was effective without the other.

There are an estimated 1.25 to 5 million Americans suffering from treatment-refractory depression (4). Feighner et al. (5) eloquently presented the case for providing nonstandard treatment when indicated, rather than abandoning these patients to their illness. Such patients, they averred, "have a moral and legitimate right to innovative therapy." Fluoxetine represents the newest of the standard antidepressants; *d*-amphetamine is one of the oldest antidepressants but is not standard. Their combination effectively benefited this patient.

REFERENCES

1. Katon W, Raskind M: Treatment of depression in the medically ill elderly with methylphenidate. *Am J Psychiatry* 1980; 137: 963-965
2. Woods SW, Tesar GE, Murray GB, et al: Psychostimulant treatment of depressive disorders secondary to medical illness. *J Clin Psychiatry* 1986; 47:210-211
3. Reimherr FW, Wood DR, Byerley B, et al: Characteristics of responders to fluoxetine. *Psychopharmacol Bull* 1984; 20:70-72
4. Pitts FN Jr: Combination drug therapy in depression (editorial). *J Clin Psychiatry* 1985; 46:205
5. Feighner JP, Herbstein J, Damlouji N: Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression. *J Clin Psychiatry* 1985; 46:206-209

LESLIE S. LINET, M.D.
Brooklyn, N.Y.

Fluoxetine and Anorgasmia

SIR: Although recognized as a side effect of trazodone (1), phenelzine, and other antidepressants (2), anorgasmia has not previously been reported in association with use of fluoxetine (3). The following cases suggest that fluoxetine at therapeutic doses may also cause anorgasmia.

Ms. A, a 35-year-old woman, was referred for treatment of obsessional and depressive symptoms. She met the *DSM-III-R* criteria for both obsessive-compulsive disorder and major depression. When first seen, she denied problems with sexual dysfunction. She was taking no medications or illicit drugs.

Three weeks after starting to take fluoxetine, 20 mg each morning, Ms. A reported that her depressive and her obsessional symptoms were markedly improved. She also reported that her pupils appeared dilated; indeed, they were large, round, equal, and reactive to light. Two weeks later, after continuing to take 20 mg of fluoxetine by mouth each morning, she had continued to improve. She reported that her obsessional symptoms were now "75% gone" and sheepishly reported difficulty in filling her newly found free time. She also reported experiencing difficulty reaching orgasm, which had progressed from relative to complete during the preceding week. Her pupils remained noticeably larger than usual.

A reduction of her fluoxetine dose to 20 mg every other day resulted in a decrease in the size of her pupils and an improvement in her sexual functioning over about 2 weeks, although she felt that it was still somewhat more difficult to reach orgasm than it had been before starting fluoxetine. Her depressive and obsessive-compulsive symptoms remained in good remission.

Mr. B, a 47-year-old man, was seen for depression associated with subjective concentration and memory impairment. He met the *DSM-III-R* criteria for major depression but not for obsessive-compulsive disorder. He denied sexual dysfunction or illicit drug use and was taking no medications.

Two weeks after starting to take fluoxetine, 20 mg/day, Mr. B was free of side effects, but his condition was only slightly improved. His dose of fluoxetine was increased to 40 mg/day; 3 weeks later, his depressive symptoms were much improved and his memory and concentration difficulties were essentially resolved. However, the patient complained of an unpleasant change in the quality of his orgasm, which had become increasingly difficult to attain. He had no erectile dysfunction or pupillary dilation. His dose of fluoxetine was reduced to 20 and 40 mg on alternating days, and his difficulty reaching orgasm subsided over about 3 weeks. His depression remained in good remission.

Both orgasm and dilation of the pupils are under control of the sympathetic branch of the autonomic nervous system, and tricyclic and other antidepressants are known to cause both pupillary dilation and anorgasmia. Fluoxetine and other serotonin uptake inhibitors inhibit methoxydimethyltryptamine-induced ejaculation in rats (4). Consistent with this preclinical evidence, the present cases suggest that fluoxetine may also cause anorgasmia, perhaps through interference with presynaptic serotonergic facilitation of sympathetic neurotransmission (5).

REFERENCES

1. Jani NN, Wise TN, Kass E, et al: Trazodone and anorgasmia (letter). *Am J Psychiatry* 1988; 145:896
2. Seagrave RT: Effects of psychiatric drugs on human sexuality, in *Psychobiology and Psychopharmacology*. Edited by Flach F. New York, WW Norton, 1988
3. Wernicke JF: The side effect profile and safety of fluoxetine. *J Clin Psychiatry* 1985; 46 (3, section 2):59-67
4. Renyi L: The effect of selective 5-hydroxytryptamine uptake inhibitors on 5-methoxy-N,N-dimethyltryptamine induced ejaculation in the rat. *Br J Pharmacol* 1986; 487:639-648
5. Adler-Graschinsky E, Butta NV, Elgoyhen AB: Serotonin uptake inhibitors and the prejunctional effects of serotonin on peripheral sympathetic nerves. *Life Sci* 1986; 39:61-68

MARK D. KLINE, M.D.
Syracuse, N.Y.

Carbamazepine for Aggressive Agitation in Demented Patients During Nursing Care

SIR: Severe aggressive actions, including kicking, biting, and striking out, are troublesome behaviors in demented patients and may be provoked only during caregiving. Conventional psychopharmacological treatments are often ineffective and/or cause unwanted sedation and other side effects during asymptomatic noncare periods.

Carbamazepine, an iminostilbene anticonvulsant, has additional efficacy in a variety of psychiatric syndromes characterized by excitation and impulsivity, including mania, episodic dyscontrol, mental retardation with overactivity, and hostile/violent psychoses. These experiences have prompted trials of carbamazepine in aggressive patients with organic mental syndrome, most of whom have been middle-aged (1, 2). This report extends clinical experience with carbamazepine to older, demented patients who are assaultive during nursing care, i.e., bathing, changing, feeding, and transferring.

Mr. A, a 70-year-old man with Alzheimer's disease, thrashed, kicked, and bit during care. Trials of low-dose haloperidol, alone and then with lorazepam (up to 1 mg b.i.d. by mouth), were ineffective and caused persistent lethargy and hypotension. Carbamazepine, titrated to 100 mg t.i.d. by mouth, with plasma levels ranging from 3 to 4 µg/ml, completely resolved his combativeness within 2 weeks.

Ms. B, a 72-year-old woman with Alzheimer's disease, was irritable and combative and shrieked and pounded, especially when receiving care. Haloperidol provoked unacceptable pseudoparkinsonism. Chloral hydrate failed to ameliorate her agitation. Two weeks of treatment with

carbamazepine, 100 mg b.i.d. by mouth, with a plasma level of 4.4 µg/ml, markedly improved her symptoms.

Mr. C, a 71-year-old man with alcoholic and multi-infarct dementia, punched, pushed, and resisted during care. His symptoms were unresponsive to trials of haloperidol and lorazepam. Carbamazepine, 100 mg b.i.d. by mouth, eradicated his symptoms in 10 days. However, leukopenia developed. The dose of carbamazepine was lowered to 100 mg/day, with continued behavioral control and normalization of the WBC count. The patient's carbamazepine blood level was 1.5 µg/ml.

Treatment of severe behavioral disturbances in demented patients often requires extraordinary or novel psychopharmacological approaches. We previously reported on the efficacy of a serotonergic combination therapy with trazodone and tryptophan in a demented octogenarian with persistent screaming and banging (3). Interestingly, aggressive behavior in four Alzheimer's disease patients has been associated with decreased brain serotonin concentrations (4). Speculative mechanisms of carbamazepine's anti-impulsive action include serotonergic modulation (5).

Carbamazepine appears to be a viable alternative in the treatment of aggressive agitation in demented patients. These cases underscore carbamazepine's versatility in treating a wide range of such behaviors during the often encountered circumstance in which outbursts are primarily precipitated by caregiving efforts. Improvements have been seen after a reasonably short period of time. Target symptoms were reduced in two of our three patients at blood levels considered subtherapeutic for seizure control, and the drug was well tolerated in the doses we used. Carbamazepine can cause leukopenia, hepatotoxicity, decreased thyroid indices, dizziness, ataxia, cardiac abnormalities, and rash, among other side effects. In fact, the development of a rash after only 4 days aborted a trial of carbamazepine in the fourth demented patient we treated. Therefore, regular medical, neurological, and laboratory monitoring is necessary. Furthermore, experience with very old patients is limited; hence, carbamazepine should be prescribed cautiously for nursing home patients.

REFERENCES

1. Essa M: Carbamazepine in dementia. *J Clin Psychopharmacol* 1986; 6:234-236
2. Patterson JF: Carbamazepine for assaultive patients with organic brain disease: an open pilot study. *Psychosomatics* 1987; 28:579-581
3. Greenwald BS, Marin DB, Silverman SM: Serotonergic treatment of screaming and banging in dementia. *Lancet* 1986; 2: 1464-1465
4. Palmer AM, Stratmann GC, Proctor AW, et al: Possible neurotransmitter basis of behavioral changes in Alzheimer's disease. *Ann Neurol* 1988; 23:616-620
5. Post RM: Mechanism of action of carbamazepine and related anticonvulsants in affective illness, in *Psychopharmacology: The Third Generation of Progress*. Edited by Meltzer HY. New York, Raven Press, 1987

DEBORAH B. MARIN, M.D.
BLAINE S. GREENWALD, M.D.
New York, N.Y.

Psychiatrists' Knowledge of Drug Costs

SIR: The high cost of medical care and patient noncompliance are both effective barriers to adequate medical treatment. It is therefore essential that physicians appreciate the costs of the care they recommend and the ability of their patients to obtain it (1). In psychiatry the limited financial resources of the chronically mentally ill may prevent patients from seeking care or buying medications (2). Many studies have shown that physicians are relatively unaware of the costs of medical treatment and that medical training does not include education on such topics (1). Fink and Kerrigan (3) demonstrated that only 27% of psychiatrists surveyed were able to give acceptable estimates of the costs of very commonly prescribed psychotropic medications. We did a similar survey and then tried an educational maneuver in an attempt to change psychiatrists' behavior.

Questionnaires asking about compliance, costs, and prescribing practices were sent to 106 psychiatrists in the Bluegrass Region of Kentucky. Those returning the questionnaire were then sent a price list of all psychotropic medications in common use. Six months later, respondents were resurveyed to assess the usefulness of the list and whether it had changed any behaviors.

Of the 106 psychiatrists surveyed, 67 (63.2%) returned the first questionnaire, and of those, 42 (62.7%) returned the second questionnaire. Most psychiatrists (75%) endorsed the belief that costs affect compliance, while few psychiatrists (19%) stated that they were aware of the costs of medication, and only a few more (37%) said that they attempt to consider costs when prescribing. One quarter knew the correct prices of four commonly prescribed drugs within 20% of the real costs. Sixty responding psychiatrists rated cost and payment modality as least important and rated the patient's previous experience as most important in choosing medications.

When resurveyed, the psychiatrists reported that they found the list informative but admitted to less than 50% utilization and change in prescribing practices. The most frequently endorsed change was advising patients to shop around; using generics and prescribing larger quantities were also endorsed.

Although this sample was limited in size and geographical location, it supports Fink and Kerrigan's earlier finding that most psychiatrists are unaware of medication costs. One could speculate that their lack of knowledge might also include costs of hospitalization, laboratory testing and procedures, and transportation, patients' loss of income due to illness or appointments, and the amount of care covered by third-party payers. This survey also suggests that although psychiatrists believe that costs affect compliance, they do little to manipulate this factor in patient care, and they may be assuming little responsibility in keeping the cost of medical care under control. These subjects should be adequately addressed in the teaching of all physicians in training. Additionally, it is necessary to change the behavior of those already in practice. Further study is needed in developing effective teaching methods and educational approaches for practitioners.

REFERENCES

1. Nagurney JT, Braham RL, Reader GG: Physician awareness of economic factors in clinical decision making. *Med Care* 1979; 17:727-736
2. Stoudemire A, Thompson TL II: Medication noncompliance:

systematic approaches to evaluation and intervention. *Gen Hosp Psychiatry* 1983; 5:233-239

3. Fink JL III, Kerrigan DJ: Physicians' knowledge of drug prices. *Contemporary Pharmacy Practice* 1978; 1:18-21

LESLEY R. DICKSON, M.D.

Lexington, Ky.

NEAL MOSER, M.D.

Cincinnati, Ohio

Wernicke's Encephalopathy Following Lithium-Induced Diarrhea

SIR: In predisposed individuals, lithium-induced diarrhea may facilitate the development of Wernicke's encephalopathy.

Mr. A, a 64-year-old retired professional, was hospitalized for psychotic depression three times over a period of 25 years. He was treated successfully with ECT the first time and with nortriptyline and ECT the second and third times. During the third hospitalization, results of tests for verbal memory were normal. As an outpatient that same year, Mr. A was started on a regimen of lithium carbonate, 600 mg/day, because he had a history of hypomanic episodes. His lithium levels averaged 0.8 meq/liter. The mild diarrhea that he had experienced occasionally before starting lithium became more frequent, with as many as eight largely uncontrollable bowel movements daily. His alcohol consumption had consisted of 2-5 oz/day of whiskey for many years.

About a year after starting to take lithium, following intensification of the diarrhea, Mr. A developed dysarthria, nausea, vomiting, confusion, and loss of recent memory. On the day before he was admitted to the hospital, his serum lithium level was 1.7 meq/liter, at which time the lithium was discontinued. He was alert and cooperative but disoriented to time. Neurological examination revealed paralysis of upward gaze, nystagmus, muscle fasciculations, dysarthria, impaired sensation in both lower extremities, wide-based gait, tremulousness, and hyperactive reflexes with clonus. His concentration was grossly impaired, and he suffered a gross loss of recent memory. He was cheerfully indifferent to this profound defect.

Thiamine, 100 mg i.v., was started on a daily basis along with intravenous fluids. Over the next 2 days, extraocular paralysis and other neurological signs improved markedly. A gross defect in verbal and visual learning remained, and confabulation was noted on repeated verbal memory tests. The patient was maintained on oral thiamine, 150 mg/day, and multiple B vitamins.

Magnetic resonance imaging (T_2 weighted, Store>11) revealed relatively increased signals in the mid pons, consistent with central pontine myelinolysis.

Two months later, the patient's memory had improved considerably according to the Rey Auditory Verbal Learning Test, but he continued to show mildly impaired learning.

Wernicke's encephalopathy is an underdiagnosed condition in living patients. Although most frequently associated with chronic alcoholism, it can be associated with any condition that affects intestinal absorption of thiamine (1). Lithium therapy may increase the risk for this condition. Diarrhea is a common side effect of lithium treatment and may

lead to impaired thiamine absorption. Patients with bipolar disorder, who constitute the major target population treated with lithium, have been noted to have a high incidence of alcohol abuse, a key etiological factor in Wernicke's encephalopathy. In addition, consideration should be given to lithium's having a direct inhibitory effect on the action of thiamine as a coenzyme, possibly through its ability to alter calcium-dependent processes (2) or through interference with the action of thiamine phosphatases in thiamine phosphorylation (3). There are a number of reports describing memory impairment associated with lithium use, but no definitive mechanism of this effect has been established (4, 5).

REFERENCES

1. Reuler JB, Girard DE, Cooney TC: Current concepts of Wernicke's encephalopathy. *N Engl J Med* 1985; 312:1035-1039
2. Meltzer HL: Lithium mechanisms in bipolar illness and altered intracellular calcium functions. *Biol Psychiatry* 1986; 21:492-510
3. Bertendorff L, Michel-Cahay C, Grandfils C, et al: Thiamine triphosphate and membrane-associated thiamine phosphatases in the electric organ of *Electrophorus electricus*. *J Neurochem* 1987; 49:495-502
4. Preodor D, Wolpert GY, Ostrow D, et al: Memory loss with lithium treatment. *Am J Psychiatry* 1977; 134:1047-1048
5. Gibbs ME, Ng KT: Psychobiology of memory: towards a model of memory function. *Biobehavioral Rev* 1979; 1:113-136

RICHARD S. EPSTEIN, M.D.
Bethesda, Md.

Tricyclics as a Possible Cause of Hyponatremia in Psychiatric Patients

SIR: In their review article "Polydipsia and Hyponatremia in Psychiatric Patients," Barbara P. Illovsky, M.D., and Darrell G. Kirch, M.D. (1) omitted reference to the role of tricyclic antidepressants as a possible cause of hyponatremia in psychiatric patients.

Ms. A, a 76-year-old woman with a chronic depressive disorder, well stabilized on a regimen of nortriptyline, 100 mg h.s., was started by her internist on amiloride, 5 mg/day, for mild hypertension. Twenty-four hours later she was brought to the emergency room because of acute onset of intermittent "confusion." On examination she was afebrile with a blood pressure of 150/80 mm Hg supine and 125/80 mm Hg sitting and a pulse rate of 80 bpm. The mucous membranes were noted to be dry. There was no jugular distention or adenopathy. Her lungs were clear on auscultation and percussion. A 1/6 systolic murmur was heard at the left sternal border. No bruits were present. Neurologic examination revealed intermittent confusion with inability to name people or objects, agitation, and inability to follow simple commands. The rest of the examination revealed no abnormalities.

On admission Ms. A had a serum sodium level of 119 meq/liter (normal range=137-144) with osmolality of 250 (normal range=280-290). Blood cultures, lumbar puncture, and a CT scan of the brain all produced normal findings. She was given a diagnosis of hyponatremia provoked by addition of a diuretic to an underlying syndrome of inappropriate secretion of antidiuretic hormone (SIADH) secondary to intake of nortriptyline. The patient was placed on intravenous normal saline with water re-

striction. Her hyponatremia was corrected over a period of 2 days. Her mental status returned to baseline as the hyponatremia resolved. She was discharged after 1 week with a serum sodium level of 138 meq/liter and mental status at baseline level.

Over the subsequent 18 months the patient continued to take nortriptyline without further diuretic medication and without recurrence of hyponatremia or confusional state. Her serum sodium levels ranged from 133 to 136 meq/liter.

While it is presumably a relatively rare phenomenon, this case illustrates the potential for tricyclic antidepressants to induce SIADH (2). In this case the effects on serum sodium were minimal, and only after administration of a diuretic was there a profound drop in the patient's serum sodium level.

With the increase in the number of elderly patients treated with tricyclic antidepressants and the high prevalence of hypertension and concomitant use of diuretics in this population, clinicians need to be sensitive to the possibility of hyponatremia with mental changes in elderly depressed patients. This is important, since tricyclics are also well-known to induce changes in mental status because of their anticholinergic side effects. Serum sodium should be assessed in patients who exhibit acute mental status changes while taking tricyclic antidepressants and diuretics.

REFERENCES

1. Illovsky BP, Kirch DG: Polydipsia and hyponatremia in psychiatric patients. *Am J Psychiatry* 1988; 145:675-683
2. Wyngaarden JB, Smith LH: Cecil Textbook of Medicine. Philadelphia, WB Saunders, 1985, p 526

MORTON G. MILLER, M.D.
Burlington, Mass.

Premenstrual Exacerbation of Bulimia

SIR: I was interested in the finding by Madeline M. Gladis, M.A., and B. Timothy Walsh, M.D. (1) of an exacerbation of binge eating and purging by female bulimic patients during the premenstrual week. As demonstrated by the work of Leon et al. (2, 3), this has not been found in all studies, and perhaps it does not occur in all bulimic patients. In my own practice, I have seen one woman who experienced an exacerbation of bulimia during her premenstrual week and one who did not.

Ms. A, a 23-year-old single woman, entered psychotherapy after experiencing severe and disorganizing anxiety on the anniversary of her mother's death. She was hospitalized briefly for evaluation and treatment and then released and treated as an outpatient. After 4 months in weekly outpatient psychotherapy, she reexperienced the bulimic behavior that she had suffered at the age of 15, alternating between extreme withholding of food and binge eating and purging. This occurred at a time when she received unwanted sexual advances and was accompanied by extreme anxiety about and distortion of her body image. She was treated with cognitive psychotherapy and encouraged to use antidepressant medication as well. She refused medication. In the 5 months after her bulimia recurred, she consistently reported that she experienced a worsening of

symptoms during the premenstrual week of her cycle. She had experienced other premenstrual symptoms since menarche, meeting the criteria for late luteal phase dysphoric disorder. She also met the criteria for a diagnosis of borderline personality disorder.

Ms. B, a 22-year-old single woman, received therapy for new-onset bulimia for 2 months. She was also in therapy for other problems when she began the episode of binge-purge behavior and experienced severe distortion of her body image. Her symptoms began to respond to therapy with tricyclic antidepressants. She did not experience premenstrual exacerbation of these symptoms and had never met the criteria for late luteal phase dysphoric disorder. She did meet the *DSM-III-R* criteria for histrionic personality disorder.

Discussion with other practitioners seems to bear out my impression that some female bulimic patients experience premenstrual exacerbation and some do not. It may be that many of those who *do* also meet the criteria for late luteal phase dysphoric disorder, but in our experience some do not.

If there is a subgroup of bulimia patients who experience premenstrual exacerbation of binge eating, this attribute may possibly be turned to therapeutic advantage. Symptoms related to an identifiable phase of the menstrual cycle may provide another opportunity to talk about the conflicted feelings many bulimic women feel about their femaleness. If premenstrual exacerbations respond to antidepressant therapy (as late luteal phase dysphoric disorder symptoms sometimes do), they may provide an observable monthly benchmark by which a patient may be able to judge her improvement over time, less hampered by the day-to-day variations in binge frequency that seem to discourage many patients when they are actually progressing.

REFERENCES

1. Gladis MM, Walsh BT: Premenstrual exacerbation of binge eating in bulimia. *Am J Psychiatry* 1987; 144:1592-1595
2. Leon GR, Phelan PW, Kelly JT, et al: The symptoms of bulimia and the menstrual cycle. *Psychosom Med* 1986; 48:415-422
3. Leon GR, Kelly JT, Phelan PW, et al: Premenstrual exacerbation of binge eating in bulimia (letter). *Am J Psychiatry* 1988; 145: 1043

WILLIAM W. MCDANIEL, M.D.
Norfolk, Va.

Psychotherapeutic Interventions for Patients With the Delusion of Having AIDS

SIR: A recent report on the delusion of having acquired immune deficiency syndrome (AIDS) in patients at low risk for AIDS (1) has prompted us to describe some of our own work with a group of these patients at our clinic. Most previous reports have been of high-risk patients, such as homosexual men, for whom a diagnosis of malingering has been made (2). Patients with "factitious AIDS," or malingerers, may be distinguished from those who present with the delusion of AIDS by virtue of their risk group and associated risk behaviors, as well as by our perception of the potential gain for patients in either case. Malingerers, on the one hand, may seek attention from health care workers, leading to invasive procedures for testing and assessment. Deluded patients, on

the other hand, may have an intense fear of death, sex, or relationships. The latter patients are, in part, similar to the "worried well" (3), who are a significant subgroup in the AIDS-psychiatric disorder spectrum. It is clear that many of the patients who present with this delusion, which may be a manifestation of an affective disorder, will improve with the appropriate medication.

In addition to the expert interventions of our liaison psychiatrists, we have found that brief psychotherapy with the patient, and sometimes the family, is advantageous. The main psychotherapeutic maneuver is to avoid getting into an impasse in which the patient protests that the therapist is not taking his or her belief about having AIDS seriously. To circumvent a situation in which views on both sides become more rigid, we have escalated the anxiety of patients in some cases (4). Thus, instead of dismissing the delusion, we ask the patient a series of hypothetical questions about the implications if indeed he or she does have AIDS. By eliciting the greatest fear, the therapist colludes with the patient in the delusion to some extent. This has the effect of altering the perception of some patients, leading to different behavior and, commonly, less rigidly held beliefs about having AIDS (5).

Worries about AIDS often conceal other problems. Marriage or sexual difficulties may be described once the delusion has been successfully dealt with. There is a role for both psychopharmacological and psychotherapeutic interventions with patients who present with the delusion of having AIDS.

REFERENCES

1. Mahorney SL, Cavenar JO Jr: A new and timely delusion: the complaint of having AIDS. *Am J Psychiatry* 1988; 145:1130-1132
2. Levine SS, Helm ML: An AIDS diagnosis used as focus of malingering. *West J Med* 1988; 148:337-338
3. Bor R, Perry L, Jackson J, et al: Strategies for counselling the "worried well" in relation to AIDS. *J R Soc Med* (in press)
4. Salt H, Perry L, Miller R, et al: Paradoxical interventions in counselling for patients with an intractable AIDS worry. *AIDS Care* (in press)
5. Miller R, Bor R: *AIDS: A Guide to Clinical Counselling*. London, Science Press, 1988

ROBERT BOR, PH.D.
RIVA MILLER, B.A.
London, England

Psychiatrists and the Management of Patients With Alzheimer's Disease

SIR: We were delighted to read the editorial by the APA Task Force on Alzheimer's Disease (1). We agree with the task force that psychiatrists have much to offer in the management (treatment may be too strong a word at this time) of Alzheimer's disease victims. Bringing their special skills to bear is quite another matter and entails several challenges; these concern diagnosis, management, and remuneration.

Psychiatrists can diagnose dementia. Determining its etiology calls for an interdisciplinary approach including at least a neurologist and a psychologist in addition to the psychiatrist. The neurologist seeks signs and symptoms of various dementia-producing entities, interprets radiologic findings, performs lumbar punctures when indicated, and suggests or carries out further studies such as EEG, carotid

Doppler studies, or, in conjunction with a radiologist, cerebral angiography.

The psychologist attempts to confirm the findings of the psychiatrist's clinical examination and attempts to determine if the deficits are localized or generalized, unilateral or bilateral, anterior or posterior. Each finding has both diagnostic and management implications.

Demented patients cannot be managed in the traditional one-to-one psychiatrist-patient relationship. Management of organically impaired patients requires additional professional help. For example, dementia victims frequently cannot be left alone while the accompanying person is being interviewed. Vital signs need to be monitored in those taking medications. Serial testing with brief psychometric instruments is needed to help determine if behavioral changes are related to progress of the dementia or other causes. Telephone calls from family members must be answered; they concern medication side effects and behavioral changes that can be monitored effectively by a nurse, thus sparing many patient visits. Psychiatrists who practice with only the assistance of a part-time secretary cannot deal effectively with these patients and their families.

Compensation for services is an important issue. At our facility, Medicare pays \$116 of the \$150 charge for an initial psychiatric evaluation and \$12 of the \$40 medication follow-up visit, despite the fact that the visit requires half an hour of a physician's and a nurse's time. Were we not part of a federally funded Alzheimer's disease research center, we could not afford to manage these patients.

The impossibility of caring for these patients as solo practitioners, the need to be part of an interdisciplinary team, and the need to find creative means to secure remuneration are all challenges to psychiatrists who wish to follow the task force's recommendations. We have found the means to accomplish these goals at our institution. A nurse coordinates patient flow and assists in evaluation and management; she is the family's chief contact. The psychiatrist, neurologist, and neuropsychologist work in concert, with the psychiatrist serving as the entry point to our system and also communicating our findings to the patients and their families. Portions of salaries are paid from our federal grant, drug studies, private philanthropy, and fees from patients.

We hope that other psychiatrists can also find means to overcome the obstacles to caring for patients with Alzheimer's disease. Doing so requires breaking down territorial barriers, sharing responsibility with other disciplines, and finding means of reimbursement to supplement poorly funded entitlement programs.

REFERENCE

1. American Psychiatric Association Task Force on Alzheimer's Disease: The Alzheimer's disease imperative: the challenge for psychiatry (editorial). *Am J Psychiatry* 1988; 145:1550-1551

MYRON F. WEINER, M.D.
JIM HOM, PH.D.
RON TINTNER, M.D., PH.D.
DORIS SVETLIK, B.S.N., R.N.
Dallas, Tex.

SIR: The editorial on Alzheimer's disease certainly made very clearly the important point that the psychiatrist is the best equipped physician to care for Alzheimer's disease patients and their families. However, the task force might have emphasized the need to explore more fully the role of the

circulation in Alzheimer's disease, since the patient in Alzheimer's original case, upon which all the subsequent, copious research on Alzheimer's disease is based, had arteriosclerosis of the radial arteries and the larger cerebral arteries (1) and also likely had some sclerosis of the carotid and vertebral arteries. This condition would tend to reduce the blood flow to the brain and impair the microcirculation, leading to neuron dysfunction.

These observations are important because anticoagulant therapy can improve the microcirculation by reducing the tendency of the blood cells to aggregate and form microthrombi. My studies over the past 25 years have shown that many dementia patients can improve tremendously and avoid nursing home care if anticoagulant therapy is combined with standard psychiatric care (2, 3). Perhaps, as Brayne and Calloway suggested (4), Alzheimer's disease is not actually a separate entity. This is worth considering in view of the implications for a far more successful treatment program than we have at present.

REFERENCES

1. Wilkins RH, Brady IA: Alzheimer's disease. *Arch Neurol* 1969; 21:109-110
2. Walsh AC: Anticoagulant therapy as a potentially effective method for the prevention of presenile dementia: two case reports. *J Am Geriatr Soc* 1968; 16:472-477
3. Walsh AC, Walsh BH, Melaney C: Senile-presenile dementia: follow-up data on an effective psychotherapy-anticoagulant regimen. *J Am Geriatr Soc* 1978; 26:467-470
4. Brayne C, Calloway P: Normal ageing, impaired cognitive function, and senile dementia of the Alzheimer's type: a continuum? *Lancet* 1988; 1:1265-1267

ARTHUR C. WALSH, M.D.
Pittsburgh, Pa.

Depression in Patients With Alzheimer's Disease

SIR: What a splendid, timely study by Burton V. Reifler, M.D., M.P.H., and associates (1) on the effects of imipramine in Alzheimer's disease patients with and without depression, and what a puzzling conclusion! "The results suggest that moderate depression is a treatable condition in patients with Alzheimer's disease." This conclusion does not startle us in terms of what we have come to accept as a truism, but the conclusion is startling if one looks at the findings of this complex, carefully documented study.

The authors treated a group of depressed and demented patients with an antidepressant. Did the depression improve? Yes. Did the "dementia" improve? Well, no; in fact, it got a little worse. A gain was offset by a loss.

One "problem" with the study is that the placebo-treated group had as much improvement in depression as the drug-treated group (and without any impairment of cognitive function). We can only conclude from this that having interest shown is of benefit to depressed, usually lonely, elderly persons.

What this study did *not* demonstrate is that a chemical—in this case, imipramine—holds the edge over "social" (my word) treatment of depression in the depressed demented elderly. (In their conclusion, the authors were careful not to attribute the improvement to the medication alone.) I had thought it did. I am grateful to the authors for a significant contribution.

REFERENCE

1. Reifler BV, Teri L, Raskind M, et al: Double-blind trial of imipramine in Alzheimer's disease patients with and without depression. *Am J Psychiatry* 1989; 146:45-49

MYRON G. SANDIFER, M.D.
Lexington, Ky.

Dr. Reifler Replies

SIR: Dr. Sandifer's reaction to the results of our study was shared by some of our investigative team, most of whom would have predicted that imipramine would prove superior to placebo.

I quite agree with Dr. Sandifer that moderate depression in a demented patient often responds quite nicely to an expression of interest and an opportunity for increased activity; I would only caution against generalizing this approach to more severely depressed inpatients, as such individuals were excluded from our study. From a personal perspective, I have not eliminated the use of antidepressant therapy in moderately depressed, demented patients, since some patients have great confidence in pharmacologic treatment, and the importance of the patient's own belief system is not to be dismissed.

One point of clarification is that we do not have enough evidence to say that our subjects' dementia worsened. Scores on the Dementia Rating Scale showed a slight decline, while scores on the Mini-Mental State showed a slight improvement; thus, the results are conflicting. However, given the potential risks of using a tricyclic antidepressant, I hope our results will encourage even biologically oriented clinicians to expand their treatment approaches to include nonsomatic forms of therapy, e.g., recommending a behavioral intervention or enrollment at an adult day center.

BURTON V. REIFLER, M.D., M.P.H.
Winston-Salem, N.C.

Disturbed Sleep in the Elderly

SIR: The review article "Sleep Disorders in the Elderly" by Michael G. Moran, M.D., and associates (1) provided a detailed, scholarly overview. There are a number of issues related to this topic that I would like to highlight further.

The authors noted that grief and mourning are common issues for the elderly that may lead to disturbed sleep. Also important is the common fear among the elderly of dying while asleep. In Greek mythology, Sleep and Death are twin brothers, Hypnos and Thanatos. We often speak of death as "the big sleep." Questions about fear of dying during sleep need to be asked of elderly patients who complain of difficulty sleeping. These fears can be addressed with psychotherapeutic interventions (2).

Another issue not specifically discussed in the article is the frequent occurrence of people in the elderly person's support network (spouse, family members, physician, nursing home personnel) who also suffer when the elderly person's sleep is disturbed. The experience in our sleep disorders program and geropsychiatry program is that it is essential to involve members of the support network in the diagnostic and treatment process. This enables us to intervene simultaneously at multiple levels of the system and to determine who is "the customer" (3). When the authors suggested a minimum of 1

month between reassessments of prescriptions for hypnotics, I become concerned that this schedule is based on what is easier for the support network or institution rather than on the patient's needs, especially since many of the hypnotic medications lose effectiveness in less than 1 month of regular nightly use (4). Unfortunately, the only rationale for prescribing hypnotic medication is often the physician's or nursing staff's wish not to have their own sleep disturbed (5).

Finally, I find it difficult to understand Dr. Moran and associates' implication that temazepam is the hypnotic agent of choice for the elderly, especially when the authors note its slow absorption and the need to take it 1-2 hours before bedtime. This could lead to the potentially dangerous situation of an elderly person taking the medication well before bedtime, forgetting he or she has taken it, and then taking additional doses. Also, taking temazepam so long before bedtime would seem to increase the likelihood of falling while trying to get to bed. My own view is that there is no perfect hypnotic agent. The clinical choice of hypnotic medication should be based on a clinical understanding of the benefits and risks of the various agents (6). The authors certainly provided us with the detailed information needed to make this choice.

REFERENCES

1. Moran MG, Thompson TL II, Nies AS: Sleep disorders in the elderly. *Am J Psychiatry* 1988; 145:1369-1378
2. Blacher RS: The briefest encounter: psychotherapy for medical and surgical patients. *Gen Hosp Psychiatry* 1984; 6:226-232
3. Lazare A, Eisenthal S, Wasserman L: The customer approach to patienthood: attending to patient requests in a walk-in clinic. *Arch Gen Psychiatry* 1975; 32:553-558
4. Kales A, Kales JD: Evaluation and Treatment of Insomnia. New York, Oxford University Press, 1984
5. Perry SW, Wu A: Rationale for the use of hypnotic agents in a general hospital. *Ann Intern Med* 1984; 100:441-446
6. Berlin RM: Management of insomnia in hospitalized patients. *Ann Intern Med* 1984; 100:398-404

RICHARD M. BERLIN, M.D.
Pittsfield, Mass.

SIR: Dr. Moran and associates advised in appendix 2 of their review that elderly patients should "avoid naps as much as possible." This advice may be premature, overly simple, and not applicable to all patients.

The authors pointed out that older persons may need daytime naps because of changes in the circadian distribution of sleep. Naps may become an important source of slow wave sleep, since slow wave sleep at night diminishes with age. Avoidance of naps may be deleterious to the patient. In an ongoing study of nap polysomnography data in elderly mental patients and control subjects (1), we found the average amount of slow wave sleep to be impressively high. In demented patients, depressed elderly subjects, and normal elderly subjects, the average values (in minutes) for slow wave sleep were 12.9, 11.5, and 10.3, respectively. Comparing these values to published data on slow wave sleep at night in these subject groups (2), we calculated that during night sleep these patients and control subjects have only 3.9, 6.3, and 9.2 minutes, respectively, of slow wave sleep. Slow wave sleep may have an important restorative value (3), and the advice to avoid daytime naps must be used with caution with the elderly, especially the demented or depressed.

REFERENCES

1. Perl E, Gurevich D, LeWitt PA, et al: Effects of tryptophan load on nap polysomnography data in demented patients and in elderly depressives. *Sleep Research* 1988; 17:295
2. Reynolds CF, Kupfer DJ, Taska LS, et al: EEG sleep in elderly depressed, demented and healthy subjects. *Biol Psychiatry* 1985; 20:431-442
3. Janssen PAJ: Does ritanserin, a potent serotonin- S_2 antagonist, restore energetic functions during the night? *J R Soc Med* 1987; 80:409-413

ELIEZER PERL, M.D.
CURTIS A. BAGNE, PH.D.
MANUEL S. DURLAO, M.D.
DAVID GUREVICH, M.D., PH.D.
DONALD F. CALDWELL, PH.D.
Detroit, Mich.

Dr. Moran and Associates Reply

SIR: While we have not found it to be "common" that elderly patients link sleep with death and that their fear of dying disrupts their sleep, Dr. Berlin's comments are interesting and worthwhile. Some elderly patients, especially those with severe medical or surgical illness, may unconsciously associate the state of helplessness connected with sleep with being out of control of their medical illness and, as in fears of impending surgery under general anesthesia, become extremely anxious. Psychotherapy that establishes these connections for the patient and then helps the patient maintain control in other areas (as a kind of compensatory gaining of control) may help.

Information from the support system of the family is crucial in the diagnosis of depression (as a cause of disrupted sleep), sleep apnea, and overuse of hypnotic agents.

Our recommendation to reassess at least monthly the need for and dose of any prescribed hypnotic medication should not be read to suggest that we consider monthly checking of the patient to be adequate care. We emphasize, first, the use of nonpharmacologic measures; next, multiple, simultaneous diagnostic approaches for a comprehensive evaluation of the complaint before prescribing any medication; and, last, close monitoring for evidence of the medication's efficacy and side effects. We feel that physicians who implement such measures are acting consonant with patients' needs.

Dr. Berlin has apparently understood our recommendation of temazepam as the agent of choice to mean that we think it is the "perfect hypnotic agent." This is a misreading of our article. Slow absorption of temazepam is a drawback but would seem to protect against the dangers (seen in rapidly absorbed agents) of rapid sedation or delirium associated with a "buzz." Anterograde amnesia can occur with any benzodiazepine, but among the hypnotics it happens most frequently with triazolam. Dr. Berlin's point about falls is well taken, especially since two recent reports have directly associated use of sedatives with a greater frequency of falls by elderly persons (1, 2). However, when specific drug classes were cited as increasing the risk of falls, short- to intermediate-acting drugs like temazepam were not mentioned; long-acting benzodiazepines seem to be the culprits.

We agree with Dr. Perl and colleagues that our advice about naps may not be applicable to all patients; increased daytime sleeping is rare (less than 2% of elderly "poor sleepers" report napping) and is chiefly an indicator only of de-

creased sleep efficiency—less sleep per nocturnal hour spent in bed—and of consequent daytime somnolence (3). However, avoiding excessive napping may help increase the demand for nighttime sleep and thereby improve distribution of sleep. A problem here is that there is notoriously little research on napping.

We disagree with the notion implied in Dr. Perl and colleagues' letter that decreased slow wave sleep in the elderly is an important deficiency that must be remedied and that naps could be the remedy. We know of no data that suggest that the decrease in slow wave sleep is pathological. Slow wave sleep consists of non-REM stages 3 and 4. Stage 4 is reduced, in both an absolute and a relative sense, with aging; stage 3 is normal or increased in women and normal or decreased in men. The changes are probably representative of decreased EEG amplitude with age, compared with that of the young adult (4).

REFERENCES

1. Ray WA, Griffin MR, Schaffner W, et al: Psychotropic drug use and the risk of hip fracture. *N Engl J Med* 1987; 316:363-369
2. Tinetti ME, Speechley M, Ginter SF: Risk factors for falls among elderly persons living in the community. *N Engl J Med* 1988; 319:1701-1707
3. McGhie A, Russell S: The subjective assessment of normal sleep patterns. *J Ment Sci* 1962; 108:642-644
4. Dement WC, Miles LE, Carskadon MA: "White paper" on sleep and aging. *J Am Geriatr Soc* 1982; 30:25-50

MICHAEL G. MORAN, M.D.
TROY L. THOMPSON II, M.D.
ALAN S. NIES, M.D.
Denver, Colo.

Heterogeneity of PTSD

SIR: The letter to the Editor on "Differences Among Patients With PTSD" by Patrick E. Ciccone, M.D., and associates (1) referred to, but contained a misinterpretation of, my work and views on posttraumatic stress disorder (PTSD). The misinterpreted quotation in their letter is, "Kolb . . . recently elaborated a neuropsychological hypothesis to explain PTSD but confined his observations to military veterans who had experienced long and high-level combat exposure."

My hypothesis applies to PTSD induced by any intense, life-threatening traumatic experience, including exposure to combat, natural disasters, and the catastrophes of daily life such as automobile, rail, and industrial accidents, fire, assault, and rape. All are perceived by the individuals exposed to them as mortal danger associated with fear/terror emotional responses. Neurologically, the CNS translates both the meaning of the percept and its intensity into electrochemical signals. My hypothesis is that often-repeated, high-intensity signals lead to neural change, which induces hypersensitivity and impairment of habituation learning. This thesis evolved not only from psychological and psychophysiological studies of combat veterans and prisoners of war but also from clinical contacts with civilian patients with PTSD. PTSD is to psychiatry as syphilis was to medicine. At one time or another, PTSD may appear to mimic every personality disorder. Life-threatening catastrophes may strike anyone, irrespective of age, sex, color, creed, health, and physical or mental disease, past or present—thus, the so-called heterogeneity. But beyond the history of the catastrophic experi-

ence, there are regularly present nuclear symptoms. These are intrusive thinking about the event(s), repetitive nightmares of the traumatic experience, startle reactions, irritability, proclivity to explosive aggressive reactions, and emotional hyperarousal when exposed to either external percepts or emergent thoughts about the event.

Depending principally on the intensity and duration of the threat experiences, the course of PTSD varies widely. One may see acute cases subsiding in a few months, others with delayed clinical onset, and the severe chronic states. Single civil accidents and industrial accidents are short-lived. These experiences do not compare in duration with the daily mortal threat experienced by the front line combat soldier or the imprisoned Holocaust victim. It is those threatened over long periods who suffer the long-standing severe personality disorganization that is episodically exacerbated in the face of current emotional stresses. Personality plays a significant role in the clinical picture as the individual struggles against recurrent fixed symptoms, responds with anxious depression, and suffers an inner devastation of his or her sense of self and security. He or she brings into operation whatever psychological defenses and assets are available. One would expect the psychophysiological changes recently described to occur particularly in those with the more severe and enduring cases of PTSD.

REFERENCE

1. Ciccone PE, Burstein A, Greenstein RA: Differences among patients with PTSD (letter). *Am J Psychiatry* 1983; 145:655-656

LAWRENCE C. KOLB, M.D.
Albany, N.Y.

Dr. Ciccone and Associates Reply

SIR: We concur with many of the ideas espoused by Dr. Kolb in his letter. For example, the heterogeneity of PTSD to which he alludes is an observation consistent with our own data. In a clinical study of more than 70 patients with acute PTSD precipitated by motor vehicle accidents and more than 150 Vietnam war veterans with chronic PTSD, we found major differences between these two groups on many variables, including source of referral, age, sex, socioeconomic level, character of intrusive and avoidance symptoms, and treatment noncompliance behavior (1).

These differences were of sufficient magnitude and quality to call into question the feasibility of constructing generalizations about PTSD based on only one treatment group. Our findings suggest that various subtypes of PTSD exist. Moreover, these differences also suggest that the character of the stressor, its timing, frequency, and duration, and the developmental age of the person on whom the stressor acts contribute to the heterogeneity of PTSD. Dr. Kolb seemingly agrees when he states that the course of PTSD varies widely depending principally on the intensity and duration of the threat experienced and, similarly, when he states that one would expect the psychophysiological changes to occur particularly in those cases which are more severe and enduring. Whether these putative psychophysiological changes occur acutely or, for that matter, precede or are consequences of psychological changes remains at issue.

Dr. Kolb's assertion that the course of PTSD varies is widely supported. A field study by Helzer et al. (2) reported

a rapid resolution of PTSD symptoms within 4-6 months after the trauma in a substantial proportion of the victims surveyed, while a less substantial group continued to have symptoms for 1 year or more. A similar clustering was noted by Burstein (3) in the duration of treatment of a group of civilians with acute PTSD.

Dr. Kolb contends that his neuropsychological hypothesis applies to PTSD induced by any intense, life-threatening traumatic experience. However, we question the import and extent of putative CNS changes that are induced by a motor vehicle accident (without direct physical injury) occurring in a time frame of seconds compared to those changes which might evolve over 1 year or more of intermittently intense combat exposure, in a prisoner of war, or in a concentration camp victim.

Although the search for biological markers of PTSD continues and includes measures as diverse as cyclic AMP signal transduction (4) and polysomnographically recorded sleep (5), the preponderance of positive biological findings has tended to come from studies of chronically stressed patients. Does Dr. Kolb's hypothesis, including attendant biological changes, apply to all subtypes of PTSD? Certainly, recapitulation of biological studies of acute cases of PTSD (e.g., victims of rape, assault, motor vehicle accidents, and natural catastrophes) would help to answer that question.

We believe that the heterogeneity of PTSD has implications for biological marker studies as well as other research. A priori attempts to establish homogeneity among PTSD research study groups for core PTSD pathology, concomitant axis I and axis II syndromes, the presence of social supports and coping skills, and a multitude of other variables would greatly enhance our understanding of what may very well be a spectrum disorder.

REFERENCES

1. Burstein A, Ciccone PE, Greenstein RA, et al: Chronic Vietnam PTSD and acute civilian PTSD: a comparison of treatment experiences. *Gen Hosp Psychiatry* 1988; 10:245-249
2. Helzer JE, Robins LN, McEvoy L: Posttraumatic stress disorder in the general population. *N Engl J Med* 1987; 317:1630-1634
3. Burstein A: Treatment length in posttraumatic stress disorder. *Psychosomatics* 1986; 27:632-637
4. Lerer B, Ebstein RP, Shestatsky M, et al: Cyclic AMP signal transduction in posttraumatic stress disorder. *Am J Psychiatry* 1987; 144:1324-1327
5. Ross RJ, Ball WA, Morrison AR: Comments on posttraumatic stress disorder (letter). *Am J Psychiatry* 1989; 146:128-129

PATRICK E. CICCONE, M.D.
Gwynedd Valley, Pa.
ALAN BURSTEIN, M.D.
Freehold, N.J.
ROBERT A. GREENSTEIN, M.D.
Philadelphia, Pa.

Prodromal Symptoms in Agoraphobia and Panic Disorder

SIR: Giovanni A. Fava, M.D., and associates (1) presented data indicating that of 20 patients suffering from panic disorder with agoraphobia, 18 reported experiencing agoraphobic avoidance, generalized anxiety, and/or hypochondriacal fears and beliefs before the first panic attack. They believe that this runs counter to the current *DSM-III-R* classification, which asserts that agoraphobia is secondary to panic

attacks (although *DSM-III-R* allows for agoraphobia without panic attacks).

The authors quoted Roth (2) in support of their findings of such prodromal features of agoraphobia. However, Roth's paper presented no systematic, study-based data; it was based on clinical observations.

The authors dismissed several studies which have found, contrary to their position, that panic attacks do precede the development of agoraphobic avoidance. Thyer and Himle (3), for example, gave questionnaires to members of an agoraphobia self-help group, asking them to date their first panic attacks and also to date when they first realized they were developing agoraphobia. The mean age at the time of the first panic attack was 25 years, whereas the mean age at the onset of agoraphobia was 33 years. However, Dr. Fava and colleagues rejected as "uncontrolled" this and other studies reporting similar data. I shall discuss their misconception of "control" below.

To explain the discrepancy between their results and those of others, Dr. Fava and colleagues suggested that there is a phenomenon of "effort after meaning," in which a patient may selectively remember events that provide an explanation for a disorder. However, it is unclear why it should be more likely for a patient to erroneously believe that his or her panic attacks cause agoraphobia than to believe that the agoraphobia causes the panic attacks.

Dr. Fava and associates' explanatory "effort after meaning" applies equally well to their own findings. For example, it is noteworthy that both their patients and their control subjects were interviewed by the same nonblind psychologist, who may have been striving after his own meaning. This elementary methodological flaw is a more convincing explanation for their discrepant results than their suggestion of "effort after meaning."

The authors favorably contrasted their easily biased, nonblind study with others they dismissed as uncontrolled, implying that their study was methodologically superior. However, the fact that they interviewed a group of normal subjects, as well as patients, to ascertain prodromal symptoms is entirely irrelevant, since the question of the *sequence* of spontaneous panic leading to phobic avoidance is a within-group, rather than a between-groups, contrast. Their so-called control group was cosmetic rather than substantive.

It is interesting that Dr. Fava and his colleagues found such a high prevalence of hypochondriasis (in 17 of 20 patients). Clinicians experienced with panic disorder patients recognize that hypochondriasis is usually secondary to panic attacks rather than an antecedent. It is possible that these investigators misinterpreted spontaneous panic attacks as hypochondriasis.

The separate, small ($N=7$) reliability study Dr. Fava and colleagues reported (correlation coefficient=0.86) did not convincingly demonstrate reliability in the detection of panic attacks. With this sample size, a generous 0.90 confidence lower limit on this correlation is 0.44, which is not reassuring.

I have never claimed that agoraphobic patients are, as the authors put it, "confident and energetic" before their first panic attack. Indeed, I have pointed out the high incidence of early separation anxiety. Whatever a patient's level of neuroticism, dependency, or fearful approach to life may be, the initial series of spontaneous panic attacks remains the key causal link that often initiates the development of the pattern of avoidances typical of agoraphobia (4).

REFERENCES

1. Fava GA, Grandi S, Canestrari R: Prodromal symptoms in panic disorder with agoraphobia. *Am J Psychiatry* 1988; 145: 1564-1567
2. Roth M: Agoraphobia, panic disorder and generalized anxiety disorder. *Psychiatr Dev* 1984; 2:31-52
3. Thyer GA, Himle J: Temporal relationship between panic attack onset and phobic avoidance in agoraphobia. *Behav Res Ther* 1985; 23:607-608
4. Klein DF, Klein HM: The nosology, genetics and theory of spontaneous panic and phobia, a critical review: II, in *The Psychopharmacology of Anxiety*. Edited by Tyrer P. New York, Oxford University Press (in press)

DONALD F. KLEIN, M.D.
New York, N.Y.

Dr. Fava and Associates Reply

SIR: In the 1960s several studies failed to show an association between life events and depression; however, these studies had considerable methodological shortcomings (1). In 1969 Paykel et al. (1) were successful in demonstrating such a relationship in a controlled study. They introduced two crucial methodological factors: 1) use of a semistructured research interview instead of an unspecific self-rating questionnaire and 2) delay of the interview until the acute disturbance had passed, to decrease the likelihood of biased recall. Two decades later, the association between life events and depression appears to have been substantiated by an impressive body of research findings (2). Research on prodromal symptoms in psychiatry is just beginning and may be at a stage that is comparable to life events studies in the 1960s. In selecting the method for our study on prodromal symptoms in panic disorder with agoraphobia, we tried to incorporate the research experience gained in studying the prodromal symptoms of schizophrenia and the advances made in life events studies (2).

Dr. Klein suggests that we implied that our study was "methodologically superior" to previous investigations because it was controlled. This is not the case—to the same extent that the issue of control did not make the investigation of Paykel et al. (1) superior to previous controlled studies on life events. First, we used a detailed, semistructured research interview instead of self-rating instruments. We do not believe that four sentences of a self-rating inventory—such as that used by Thyer and Himle and mentioned by Dr. Klein—and a 1-hour interview with detailed probing and cross-checking with relatives are likely to yield similar results. This would contradict two decades of psychometric research. Life events research (2) has shown that the "effort after meaning" particularly applies to ill-defined and vague enquiries.

Dr. Klein wonders "why it should be more likely for a patient to erroneously believe that his or her panic attacks cause agoraphobia than to believe that the agoraphobia causes the panic attacks." The dramatic, sudden occurrence of panic attacks lends itself to effort after meaning more than the subtle, slow development of agoraphobic avoidance. Any clinician experienced in behavioral treatment of phobic disturbances is aware that patients are likely to deny phobic disturbances and tend to become fully aware of them in the course of treatment, when they are actually confronted with the feared situations or objects. Postponing the research interview until the acute disturbance has passed was therefore the second, crucial methodological issue.

We would like to reassure Dr. Klein that we are able to discriminate between hypochondriasis and panic attacks. It is worth mentioning, however, that current diagnostic instruments (e.g., the Schedule for Affective Disorders and Schizophrenia) do not include enough information on hypochondriacal fears and beliefs (for instance, they do not discriminate between hypochondriasis, nosophobia, concern about pain, etc.). This is why we had to incorporate Kellner's Illness Attitude Scales in Paykel's Clinical Interview for Depression. The interview, which we have been using for 8 years, and the small reliability study were not aimed at detecting panic attacks, as Dr. Klein implies, but were for rating prodromal symptoms only.

The fact that our study was controlled was not for "cosmetic" reasons. A control group would have been unimportant for a negative study. In our case, however, we wanted to verify whether our sensitive instrument might yield false positive results in a sample of normal subjects, as we had found with the Hamilton Rating Scale for Depression.

Dr. Klein did indeed write that patients are "often feeling quite well" when they are suddenly struck by the worst experience of their lives, a panic attack (3, p. 236). We are glad to see that his views on the pre-panic patient are changing.

When we wrote our report, there were no published studies to support our findings, aside from Roth's clinical wisdom. Since then, two investigations have provided some support for our results, even though their methods are still subject to criticism. Garvey et al. (4) found that 28% of 32 panic disorder patients had prodromal generalized anxiety symptoms lasting a median of 5 years before the occurrence of the first panic attack. Lelliott et al. (5) reported that 70% of 56 patients with panic disorder had prodromal depression, anxiety, or avoidance in the month before the first panic attack. Agoraphobic avoidance preceded the first panic in 23% of cases.

Will the primacy of panic attacks in agoraphobia (and thus of panic disorder with agoraphobia compared to agoraphobia with panic attacks) survive the test of time? We think our investigation has yielded methodological stimuli for further progress in the area of research on prodromal symptoms. Meanwhile, more and more clinicians are becoming aware of the limitations of treating the symptoms (panic) as the whole disease (agoraphobia).

REFERENCES

1. Paykel ES, Myers JK, Dineen MN, et al: Life events and depression. *Arch Gen Psychiatry* 1969; 21:753-760
2. Brown GW, Harris T: Establishing causal links: the Bedford College studies of depression, in *Life Events and Psychiatric Disorders*. Edited by Katschinig H. London, Cambridge University Press, 1986
3. Klein DF: Anxiety reconceptualized, in *Anxiety: New Research and Changing Concepts*. Edited by Klein DF, Rabkin J. New York, Raven Press, 1981
4. Garvey MJ, Cook B, Noyes R: The occurrence of a prodrome of generalized anxiety in panic disorder. *Compr Psychiatry* 1988; 29:445-449
5. Lelliott P, Marks I, McNamee G: Onset of panic disorder with agoraphobia. *Arch Gen Psychiatry* (in press)

GIOVANNI A. FAVA, M.D.
SILVANA GRANDI, M.D.
RENZO CANESTRARI, M.D.
Bologna, Italy

Effect of Fluoxetine on Metabolism of Tricyclic Antidepressants in the Lungs

SIR: The recent letter to the Editor by D.A. Vaughan, M.D. (1) on increased blood levels of tricyclics associated with use of fluoxetine reported a very important finding. The mechanism of this interaction is unknown. Dr. Vaughan suggested that fluoxetine may inhibit the hepatic metabolism of tricyclics. However, the data on one of her patients seem inconsistent with this hypothesis. Therefore, I would like to offer other possible mechanisms to account for this interaction.

Dr. Vaughan's second patient, Ms. B, only took 20 mg of fluoxetine for 3 days, yet her desipramine level rose to almost five times the previous level (to 632 ng/ml). Unfortunately, the report did not tell us how long the fluoxetine had been discontinued before this plasma level was reached; we can only surmise that it was several days later. Furthermore, the possible side effects that developed with fluoxetine seem to have lasted several weeks. If these were the result of an elevated plasma level of the tricyclic, this would indicate that only 3 days of fluoxetine treatment produced an adverse reaction with a tricyclic that lasted for several weeks. It seems unlikely that fluoxetine, with a half-life of only 1-3 days (2), would produce such a prolonged reaction through a hepatic mechanism. However, fluoxetine's *N*-demethylated metabolite, norfluoxetine, has a plasma half-life of 7-15 days (2). Therefore, this metabolite would be more likely to cause a prolonged tricyclic level by inhibiting the hepatic metabolism of the tricyclic.

However, we would like to suggest another site for this interaction: the lungs. Radiolabeled fluoxetine and norfluoxetine have persisted in the human body for more than 20 days (2). Interestingly, in animals, fluoxetine and norfluoxetine are sequestered in tissue (primarily lung tissue) and very slowly disappear upon discontinuation of fluoxetine (2). Tobacco smoke contains inhibitors and inducers of drug-oxidizing enzymes and, in some studies, has been shown to lower plasma concentrations of tricyclic antidepressants (3). This net effect of stimulation of drug metabolism probably occurs in the lungs, not the liver (3). Therefore, if fluoxetine and its metabolites are stored in the lungs, fluoxetine's possible effect on metabolism of tricyclics may occur here rather than in the liver. Fluoxetine and/or its metabolites may inhibit tricyclic-oxidizing enzymes in the lungs, thereby causing prolonged elevated plasma levels of the tricyclic.

Also, if fluoxetine and its metabolites are stored in the lungs in humans, it becomes vital to know whether Dr. Vaughan's patients were smokers. Possibly, tobacco smoke affects the metabolism of fluoxetine in the lungs. Therefore, it is conceivable that both fluoxetine and tobacco smoke must be present to cause the elevated tricyclic levels. We have one patient who becomes ill (generalized weakness, lethargy, and lightheadedness) if he smokes while taking 40-60 mg/day of fluoxetine. This reaction does not occur if he chews nicotine gum instead of smoking. This indicates that the tobacco smoke may somehow contribute to this reaction, possibly by affecting metabolism of fluoxetine. It is important to remember that tobacco smoking may have an effect on drug-metabolizing enzymes which lasts for 3 months or more after cessation of smoking (4).

REFERENCES

1. Vaughan DA: Interaction of fluoxetine with tricyclic antidepressants (letter). *Am J Psychiatry* 1988; 145:1478
2. Lemberger L, Bergstrom RF, Wolen RL, et al: Fluoxetine: clin-

- ical pharmacology and physiologic disposition. *J Clin Psychiatry* 1985; 45(3, section 2):14-19
3. Rudorfer MV, Potter WZ: Pharmacokinetics of antidepressants, in *Psychopharmacology: The Third Generation of Progress*. Edited by Meltzer HY. New York, Raven Press, 1987
 4. D'Arcy PF: Tobacco smoking and drugs: a clinically important interaction? *Drug Intell Clin Pharm* 1984; 18:302-307

JOHN M. DOWNS, M.D.
ANNA D. DOWNS, PH.D.
Memphis, Tenn.

Dr. Vaughan Replies

SIR: I appreciate the suggestion by Drs. John and Anna Downs that fluoxetine and its metabolite norfluoxetine may be sequestered in lung tissue and that tobacco smoke might affect the metabolism of fluoxetine in the lungs. However, neither Ms. A nor Ms. B in my case reports smoked cigarettes; therefore, the proposed mechanism does not explain the elevated plasma levels of the tricyclic antidepressant.

D. ANN VAUGHAN, M.D.
Wichita, Kan.

Subtyping Dysthymia

SIR: In their article "A Critical Discussion of *DSM-III* Dysthymic Disorder" (1), James H. Kocsis, M.D., and Allen J. Frances, M.D., proposed three subtypes of chronic depression. One subtype has an early, insidious onset followed by a course that may or may not progress to intermittent or chronic depression of major proportions. A second subtype of intermittent or chronic depression may develop after an acute major depression, often at a later age. A third type appears to be chronic depression in association with other axis I or axis II psychopathology, a chronic medical disorder, or chronic stress. The authors' subcategorization seems important, especially with respect to the clinical picture.

When we classified 80 inpatients (40 of them male) according to their clinical picture, we found the following. There were 13 inpatients (16.3%) of subtype 1, eight inpatients (10%) of subtype 2, and 59 inpatients (73.8%) of subtype 3. These results reveal an excessive number of patients in subtype 3. Nine (15.3%) of the inpatients in this subtype (seven female and 2 male) had only somatization disorder and dysthymia.

According to *DSM-III-R*, anxiety and depressed mood are extremely common, and many individuals with somatization disorder seek health care because of depressive symptoms, including suicide threats and attempts. In a study that was part of the National Institute of Mental Health Epidemiologic Catchment Area Program used to examine somatization disorder in a community population, Swartz et al. (2) reported a high association between depression (major depression and dysthymia) and somatization disorder. Approximately 65% of the respondents who had somatization disorder according to the Diagnostic Interview Schedule and *DSM-III* also met the criteria for dysthymic disorder. They also found that 77.96% of those with somatization disorder had more than one diagnosis. Somatization disorder is diagnosed predominantly in women (2, 3).

Considering these data and our results, we may at least consider the patients with somatization disorder as a distinct fourth subgroup. But we also should not neglect the need for

further research concerning diagnoses on all five axes in a widened group of dysthymic patients so as to achieve better subcategorization.

REFERENCES

1. Kocsis JH, Frances AJ: A critical discussion of *DSM-III* dysthymic disorder. *Am J Psychiatry* 1987; 144:1534-1542
2. Swartz M, Blazer D, George L, et al: Somatization disorder in a community population. *Am J Psychiatry* 1986; 143:1403-1408
3. Cloninger CR, Martin RL, Guze SB, et al: A prospective follow-up and family study of somatization in men and women. *Am J Psychiatry* 1986; 143:873-878

CAN TUNCER, M.D.
K. OĞUZ KARAMUSTAFALIOĞLU, M.D.
Istanbul, Turkey

Dr. Kocsis Replies

SIR: Drs. Tuncer and Karamustafalioglu raise an important issue about dysthymia that was only partly addressed in our review. Dysthymic disorder has been found to have a high comorbidity with other axis I disorders (1). Should dysthymic patients who have comorbid somatization disorder, psychoactive substance abuse disorder, eating disorders, etc. be categorized as separate subtypes? Such a suggestion would seem premature until more data are available about the course, family history, and treatment response in groups having or not having somatization disorder or other comorbid conditions. It will be important to systematically diagnose comorbid disorders and to gather data about implications for classification and treatment. Drs. Tuncer and Karamustafalioglu are to be commended for making this effort and for drawing attention to this issue.

REFERENCE

1. Weissman MM, Leaf PJ, Bruce ML, et al: The epidemiology of dysthymia in five communities: rates, risks, comorbidity, and treatment. *Am J Psychiatry* 1988; 145:815-819

JAMES H. KOCSIS, M.D.
New York, N.Y.

Converting Doses of Fluphenazine Decanoate to Oral Equivalents

SIR: We found the article by Lawrence B. Inderbitzin, M.D., and colleagues (1) regarding dosage of fluphenazine decanoate troubling because their conclusions may be misleading. Essentially, the authors retrospectively studied two groups of 20 schizophrenic patients. One group received fluphenazine decanoate and the other received only oral medication. There were no demonstrable differences in any other clinical or demographic characteristics. The authors then calculated the amount of oral chlorpromazine equivalents prescribed for each group by using a conversion factor for fluphenazine decanoate which we believe is unproven at best and invalid at worst. They concluded that patients receiving decanoate were taking very high levels of neuroleptic compared to those receiving oral medication. The authors' clear message was that patients taking decanoate were likely receiving much higher doses of medication than they required.

The troubling part of this study is that it was entirely based on a conversion factor from decanoate to chlorpromazine equivalents which is less widely accepted than the authors suggested. According to the equation they presented, 25 mg (1 cc) of fluphenazine decanoate every 2 weeks equals 1500 mg/day of chlorpromazine equivalents. Many other researchers (2-5) have stated that this dose of fluphenazine decanoate is approximately equal to between 200 and 800 mg/day of chlorpromazine equivalents. This means that the data of Dr. Inderbitzin and associates may be off by a factor of 2 to 7, which would essentially eliminate differences between patients taking oral medication and those taking the depot medication.

Most clinicians and researchers would agree that there is no definitive way to convert depot medication doses into oral equivalents, but there is no mention of this problem in the article. The results of this study might not be as definitive as they appear.

Indeed, an alternative interpretation of the data is that since the two groups of schizophrenic patients were indistinguishable on all measures (including positive and negative symptoms of schizophrenia), perhaps they were receiving equivalent doses of medication, but the conversion factor resulted in spurious statistical conclusions.

We certainly support the notion that neuroleptics should be used at minimum effective doses. Carefully controlled reductions in both oral and intramuscular doses are warranted. However, the problems in statistically converting intramuscular decanoate to oral equivalents may have led to unwarranted conclusions in this study.

REFERENCES

1. Inderbitzin LB, Lewine RRJ, Gloersen BA, et al: Fluphenazine decanoate: a clinical problem? *Am J Psychiatry* 1989; 146:88-91
2. Baldessarini RJ: *Chemotherapy in Psychiatry*. Cambridge, Mass, Harvard University Press, 1985, p 36
3. Chien C-P, Cole JO: Depot phenothiazine treatment in acute psychosis: a sequential comparative clinical study. *Am J Psychiatry* 1973; 130:13-18
4. Mason AS, Granacher RP: *Clinical Handbook of Antipsychotic Drug Therapy*. New York, Brunner/Mazel, 1980, pp 36-37
5. Hollister LE: *Psychiatric disorders*, in *Avery's Drug Treatment*, 3rd ed. Edited by Speight TM. Baltimore, Williams & Wilkins, 1987

ANDREW W. BROTMAN, M.D.
SCOTT MCCORMICK, M.D.
Boston, Mass.

Drs. Inderbitzin and Lewine Reply

SIR: We agree that there are no satisfactory data on which to determine an absolutely definitive conversion formula and acknowledge that other authors have used other equivalences, although it is not always clear how they arrived at them. The formula we used is based on the National Institute of Mental Health Psychopharmacology Research Branch multicenter study of fluphenazine equivalence reported by Schooler and Levine (1). In addition to being cited in *Drug Facts and Comparisons* for 1984 and 1989 (2, 3), the formula is the one recommended by the original and principal manufacturer of fluphenazine decanoate. Furthermore, we reported not only the conversion formula we used but also

the actual doses of fluphenazine decanoate per unit of time, so that readers could decide for themselves.

Drs. Brotman and McCormick contend that our use of this formula "may have led to unwarranted conclusions." It is at least equally plausible that other methods of conversion have inadvertently obscured an important clinical issue regarding dissimilar dosing with high-potency and low-potency neuroleptics. Baldessarini et al. (4) first called attention to this: "The mean chlorpromazine-equivalent dose of popular potent agents (haloperidol or fluphenazine) was 3.54 times as high as that of popular low-dose agents (chlorpromazine or thioridazine). Potent agents are commonly used in mania and schizophrenia, often in relatively high doses, which may carry an excess of risk over unproven added benefit." Our findings point in the same direction, and we believe that this issue has not received sufficient attention.

It is one thing to state support for prescribing neuroleptics at minimum effective doses, but quite another to critically examine our actual practices. We hope other investigators will agree that this is an interesting and challenging area for further research.

REFERENCES

1. Schooler NR, Levine J: The initiation of long-term pharmacotherapy in schizophrenia: dosage and side effect comparisons between oral and depot fluphenazine. *Pharmakopsychiatr Neuropsychopharmacol* 1976; 9:159-169
2. *Drug Facts and Comparisons*, 1984. St Louis, JB Lippincott, Facts and Comparisons Division, 1983, p 966
3. *Drug Facts and Comparisons*, 1989. St Louis, JB Lippincott, Facts and Comparisons Division, 1988, p 1100
4. Baldessarini RJ, Katz B, Cotton P: Dissimilar dosing with high-potency and low-potency neuroleptics. *Am J Psychiatry* 1984; 141:748-752

LAWRENCE B. INDERBITZIN, M.D.
RICHARD R.J. LEWINE, PH.D.
Atlanta, Ga.

Classification of Patients Not Meeting *DSM-III-R* Criteria for Schizophrenia

SIR: Wayne S. Fenton, M.D., and associates (1) reported that application of the *DSM-III-R* criteria for schizophrenia results in the exclusion of approximately 10% of individuals diagnosed as schizophrenic according to *DSM-III*. These patients have to be reclassified as suffering from atypical psychosis. They have symptoms of a delusional (paranoid) disorder but do not meet the *DSM-III-R* requirements for that disorder. I think the authors have demonstrated an inadvertent but useful outcome of the change to *DSM-III-R*.

As an erstwhile member of the *DSM-III-R* Psychosis Committee, I concurred with the fine-tuning process for schizophrenia and was delighted with the much-needed revision of the *DSM-III* paranoid disorders section. However, I believe that *DSM-III-R*'s definition of delusional (paranoid) disorder is overly restrictive (2). It quite accurately describes Kraepelinian paranoia (a monodelusional disorder) but ignores Kraepelinian paraphrenia, although many psychiatrists are convinced of the existence of this disorder. Paraphrenia is well-described in *ICD-9*, but, unfortunately, it may be dropped from *ICD-10* (1987 draft of chapter V), apparently to promote uniformity with *DSM-III-R*. Its absence from

DSM-III-R means that cases currently have to be consigned to the grab-bag diagnosis of atypical psychosis.

We have no accurate figures for the frequency of paraphrenia in an inpatient population. Dr. Fenton and his colleagues may now have provided an approximation, if we can conclude that most of their excluded cases are delusional disorders of the paraphrenic, rather than the paranoid, type. If we do this, we can "guesstimate" that paraphrenia (*ICD-9*) is about one-tenth as common among inpatients as schizophrenia defined according to *DSM-III-R*.

Without reading more than is warranted into this aspect of their study, I would urge Dr. Fenton and his colleagues not to bemoan the changes regarding the diagnostic criteria for schizophrenia in *DSM-III-R* but to consider the possibility that they have found a way to separate out a subgroup of cases which did not properly belong with schizophrenia in the first place.

Although they are real illnesses, paranoia and paraphrenia have languished unjustifiably in obscurity. Paranoia, thanks to *DSM-III-R*, is now becoming more readily recognized in North America. Paraphrenia will follow suit, although its nonappearance in *DSM-III-R* will slow the process of conceptualization and case recognition. I believe that if other workers were to duplicate Dr. Fenton and associates' investigation and look more closely at the excluded patients they described, they would find that this is not a chance collection of patients with heterogeneous conditions but a relatively homogeneous group worthy of separate study.

REFERENCES

1. Fenton WS, McGlashan TH, Heinssen RK: A comparison of *DSM-III* and *DSM-III-R* schizophrenia. *Am J Psychiatry* 1988; 145:1446-1449
2. Munro A: Paranoid (delusional) disorders: *DSM-III-R* and beyond. *Compr Psychiatry* 1987; 28:35-39

ALISTAIR MUNRO, M.D., F.R.C.P.(C)
Halifax, N.S., Canada

Dr. Fenton and Associates Reply

SIR: Perhaps, as Dr. Munro points out, we have stumbled upon Kraepelin's paraphrenia among patients diagnosed as schizophrenic according to *DSM-III* who are no longer considered schizophrenic according to the criteria of *DSM-III-R*. However, we demonstrated that this group's baseline clinical characteristics and long-term course *did not differ* in any way (except by the defining symptom criteria) from those of the group diagnosed as schizophrenic according to *DSM-III-R*. Therefore, if we have demonstrated paraphrenia, we have also demonstrated a justification for its exclusion from the nosology. If at some time in the future "paraphrenic" and "schizophrenic" patients are shown to differ in relation to pattern or degree of inheritance, developmental history, brain morphology, biochemical markers, neurophysiologic functioning, course of illness, treatment response, or any other external validating criterion, we would favor rescuing paraphrenia from obscurity. By our analysis of descriptive and predictive validity, however, paraphrenia (if that is the diagnosis our excluded group

might be given) and schizophrenia appear to be the same entity.

WAYNE S. FENTON, M.D.
THOMAS H. MCGLASHAN, M.D.
ROBERT K. HEINSEN, PH.D.
Rockville, Md.

Neural Substrate of Empathic Communication

SIR: Leslie Brothers, M.D. (1) has related the role of the right hemisphere in empathy to the production and understanding of the affective components of language. This may be analogous to the active imagining and passive echoing that compete and augment empathy (2). These components may be monitored by speech pause time, a behavioral correlate of mood, which measures precisely cues such as motility, affective expression, and tempo (3). Pause time, at least in manual activity, is linked to the right hemisphere (4), as are both the sequencing of elements after motor response is initiated (5) and the shape attributes in freehand expression, which are right central in origin (6). These data provide a needed basis for framing hypotheses regarding the neural substrate of empathic communication by manual and speech expressions.

REFERENCES

1. Brothers L: A biological perspective on empathy. *Am J Psychiatry* 1989; 146:10-19
2. Margulies A: Toward empathy: the uses of wonder. *Am J Psychiatry* 1984; 141:1025-1033
3. Friedman EH, Sanders GG: Speech pattern analysis, in *Encyclopedia of Medical Devices and Instrumentation*. Edited by Webster JG. New York, John Wiley & Sons, 1988
4. Friedman EH: More on Hitler and Parkinson's disease (letter). *N Engl J Med* 1987; 316:114
5. Sivak B, MacKenzie CL: Evidence for cerebral asymmetries in a sequencing task. *Brain Cogn* 1989; 9:109-122
6. Grossman M: Drawing deficits in brain-damaged patients' free-hand pictures. *Brain Cogn* 1988; 8:189-205

ERNEST H. FRIEDMAN, M.D.
East Cleveland, Ohio

Dr. Brothers Replies

SIR: Dr. Friedman's letter addresses the interesting issue of the temporal features of expressive activity. By implication, he raises the issue of the neural basis of their detection by a receiver.

Precise measurement of pause and "dialogue" epochs in mother-infant interactions has been carried out by Beebe and Lachmann (1). They showed that infants 3-4 months of age establish expectations regarding the rhythm of social exchanges and, together with their caregivers, perform stable pause-and-activity sequences. What is of interest in regard to the development of empathy is that the infants' representations of tempo appear to be based on the activity of the dyad rather than on that of either individual; furthermore, the performances of both mother and infant ensure that a joint, mutually responsive rhythm is maintained. A comprehensive account of the neural basis of empathy must encompass these findings, which are suggestive not so much of mimicry as of participatory matching.

Additionally, from the general point of view of higher cortical function, it is striking that a sophisticated ability to organize events in the temporal domain is present in young infants.

REFERENCE

1. Beebe B, Lachmann FM: The contribution of mother-infant mutual influence to the origins of self- and object representations. *Psychoanal Psychol* 1988; 5:305-337

LESLIE BROTHERS, M.D.
Pasadena, Calif.

Corrections

In the review by Peter Ostwald, M.D., of the book *Turn-of-the-Century Cabaret: Paris, Barcelona, Berlin, Munich, Vienna, Cracow, Moscow, St. Petersburg, Zurich*, by Harold B. Segel (December 1988 issue, pp. 1602-1603), the name of Klaus Kerblinger, M.D., was given incorrectly as Klaus Kerblinger.

In the letter to the Editor "Suicidal Tendencies in Women With Human Immunodeficiency Virus Infection" from George R. Brown, M.D., and James R. Rundell, M.D. (April 1989 issue, pp. 556-557), the reference citation on page 557 on the eighth line from the end of the letter should read "(4)." Also, reference 5 should begin "Kolb LC."

Reprints of letters to the Editor are not available.

**AMERICAN
PSYCHIATRIC
ASSOCIATION**

A message to psychiatrists and employers

Simplify your search for the right job or job candidate. Let the professional resources of APA's Psychiatric Placement Service work for you.

If you are a psychiatrist seeking a new challenge, a better location, or a more lucrative salary, the Psychiatric Placement Service will put you in touch with suitable employers. For a modest fee and in complete confidence, you can list your professional qualifications and your personal preferences with the PPS for one year.

As an employer, you will benefit from the experience of professional recruiters who will carefully explore every aspect of your position and match your requirements against a comprehensive pool of physician candidates. Unlike other search firms, the PPS puts at your disposal the wide resources of APA—all for a fraction of the cost you might expect.

In its first year, the Psychiatric Placement Service successfully introduced many qualified candidates to prospective employers. This year, we'd like to introduce you to your next employment opportunity. Call Graeme Fergusson at (202) 682-6108 or mail this coupon today.

Please send me more information about the Psychiatric Placement Service.

☐ Potential
Applicant

☐ Potential
Employer

Name (please print) _____

Address _____

City _____

State _____

Zip _____

Phone _____

Mail to Graeme Fergusson, Placement Coordinator,
Psychiatric Placement Service, APA, 1400 K Street, N.W.,
Washington, D.C. 20005

**Psychiatric
Placement
Service**

*Fully staffed and operated by the Hospital &
Community Psychiatry Service of the American
Psychiatric Association*

Where's the best place for a patient recovering from a drug or alcohol problem?...

THE BRITISH JOURNAL OF PSYCHIATRY

APRIL 1989

VOLUME 154

Annotation

- Sight and insight: brain dopamine receptor occupancy by neuroleptics visualised in living schizophrenic patients by positron emission tomography. *J.L. Waddington* 433

Review Articles

- Seclusion. *A. Angold* 437
Psychotherapy and general practice. *L. Gask and G. McGrath* 445

Comment

- The toxicity of antidepressants. *G. Beaumont* 454

Lecture

- The varieties of human experience. *J.C. Nemiah* 459

Papers

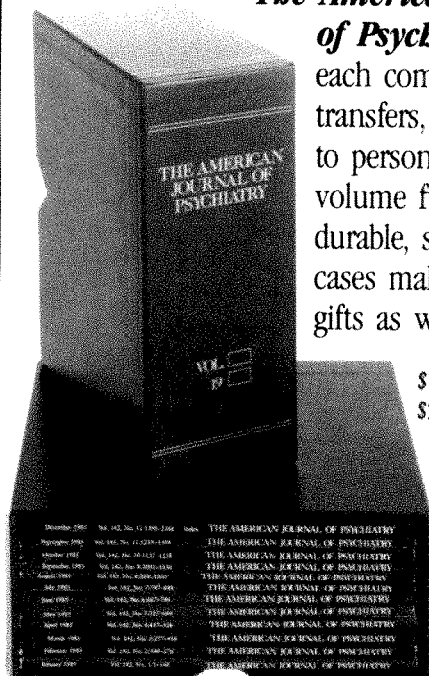
- The classification of functional psychoses and its implications for prognosis. *H.J. Möller, M. Hohe-Schramm, C. Cording-Tömmel, W. Schmid-Bode, H.U. Wittchen, M. Zaudig and D. von Zerssen* 467
Family therapy influences on general adult psychiatry. *D. Cottrell* 473
Social support and the outcome of major depression. *L.K. George, D.G. Blazer, D.C. Hughes and N. Fowler* 478
The nature and prevalence of depression in chronic schizophrenic in-patients. *T.R.E. Barnes, D.A. Curson, P.F. Liddle and M. Patel* 486
The Scottish first episode schizophrenia study. VI. Computerised tomography brain scans in patients and controls. *The Scottish Schizophrenia Research Group, H.L. MacDonald and J.J.K. Best* 492
Factors associated with the course and outcome of schizophrenia in India: results of a two-year multicentre follow-up study. *A. Verghese, J.K. John, S. Rajkumar, J. Richard, B.B. Sethi and J.K. Trivedi* 499
Psychiatric disorders among medical in-patients in an Indian hospital. *S.N. Deshpande, K.R. Sundaram and N.N. Wig* 504
The psychiatrist in the obstetric unit: establishing a liaison service. *L. Appleby, H. Fox, M. Shaw and R. Kumar* 510
Psychological aspects of hysterectomy: a prospective study. *M.M. Ryan, L. Dennerstein and R. Pepperell* 516
The course of tardive dyskinesia in patients on long-term neuroleptics. *J.A. Bergen, E.A. Eyland, J.A. Campbell, P. Jenkins, K. Kellehear, A. Richards and P.J.V. Beaumont* 523
Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone. *S.M. Murphy, R. Owen and P. Tyrer* 529
Significance of extreme temperament in infancy for clinical status in pre-school years. I: Value of extreme temperament at 4–8 months for predicting diagnosis at 4.7 years. *M. Maziade, R. Côté, H. Bernier, P. Boutin and J. Thivierge* 535
Significance of extreme temperament in infancy for clinical status in pre-school years. II: Patterns of temperament change and implications for the appearance of disorders. *M. Maziade, R. Côté, H. Bernier, P. Boutin and J. Thivierge* 544
Brief Reports
Capgras' syndrome and folie à deux involving mother and child. *J. Hart and G.M.G. McClure* 552
Epilepsy and arson. *P.K. Carpenter and A.L. King* 554
Altered state of consciousness in a compulsive water drinker. *S. Lee, C.C. Chow and L.C.L. Lee* 556
Psychotic illness following termination of pregnancy. *K. Davidson and A.W. Clare* 559
The neuroleptic malignant syndrome and pneumomediastinum. *B.H. Green* 560
Zuclopenthixol-induced neuroleptic malignant syndrome at rechallenge and its extrapyramidal effects. *C.J.C. Kemperman* 562
Correspondence 564
A hundred years ago. *Researched by Henry Rollin* 578
Book Reviews 579

Preserve your copies of *The American Journal of Psychiatry*

Custom-made for the *Journal*, these slipcases turn back issues into a permanent reference source. Bound in attractive green leatherette, and embossed with gold lettering, each slipcase holds one year (12 issues) of

The American Journal of Psychiatry

And each comes with gold transfers, allowing you to personalize your volume further. These durable, space-saving cases make affordable gifts as well.



\$7.95 each, three for \$21.95, six for \$39.95.

Add \$1.00 per unit for postage and handling.
(Outside U.S. add \$2.50 per unit. U.S. currency only.)
PA residents add 6% sales tax.

Mail to: **The American Journal of Psychiatry**

Jesse Jones Industries
Dept. AJP
499 East Erie Avenue
Philadelphia, PA 19134

Please send me _____ slipcases.

☐ Enclosed is my check or money order for \$ _____

☐ Charge my _____ American Express

_____ Visa

_____ MasterCard

_____ Diners Club

(\$15 minimum charge order)

Card # _____ Exp. Date _____

Interbank # _____

Signature _____

TOLL FREE CHARGE ORDERS: 1-800-972-5858

Name _____
(please print)

Address _____
(no P.O. boxes please)

City/State/Zip _____

Satisfaction guaranteed.

...on the job.

When your patient hesitates to enter a 28-day addiction treatment program because of family or job pressures, you now have an alternative. It's the CAREER™ program at Philadelphia Psychiatric Center.

CAREER is a *true* partial hospitalization program. Patients undergo two weeks of intensive 12-hour treatment days. Several more weeks of concentrated outpatient treatment follow—up to five evenings a week.

And, a special treatment feature lets your patient attend evening therapy sessions anytime he or she needs extra support. For a full year and at no cost.

When you admit a patient to CAREER, we consult with you to develop the optimum treatment plan, which can incorporate therapy sessions with you. We also provide timely progress updates.

The CAREER program works. Our patient recovery rate compares with full-time programs.

For more than 50 years, we've helped people return to normal, productive lives. CAREER continues that tradition.

For more information, please call at 215-473-8000.

**PHILADELPHIA
PSYCHIATRIC
CENTER**



A subsidiary of Albert Einstein,
genius in healthcare.



APA LIBRARY AND ARCHIVES

Answers to Questions Our Members Often Ask

Where is the Library and Archives?

The Library and Archives is on the third floor of the APA headquarters building at 1400 K Street N.W., Washington, D.C. The hours are 9 am to 5 pm Monday through Friday.

How can I use the Library and Archives?

You can request information by mail, telephone or personal visits.



Can I borrow books?

APA members (and cooperating libraries) may borrow books at no charge. The normal loan period is 4 weeks.

Can I get reprints of journal articles from the Library?

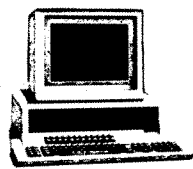
No. Reprints are available from authors. Libraries can only supply photocopies. We encourage you to make use of local sources for journals, but we will photocopy articles from our collection at the pre-paid cost of \$3 to members.

Is there a number I can call for answers?

Yes. (202) 682-6058 is the reference number. We try to answer questions right away, but sometimes we need time to gather information. We can usually respond within 24 hours.

Does the Library do computer searching?

Yes. (202) 682-6057 is the number to call to request a computer literature search. Because search requests require a signed form, it's a good idea to keep a supply on hand. Call and ask us to send some for your next project. Charges for members are cost plus



\$15; non-members, cost plus \$40. Turnaround time is 2 weeks. Records retrieved include full bibliographic citations and in most cases abstracts.

Can you help me find an article in *Psychiatric News*?

Yes. Call (202) 682-6080. The APA Library provides the only in-depth indexing service for *Psychiatric News*. There is complete coverage since 1978.



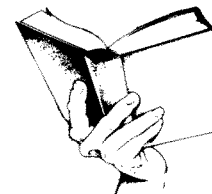
Does the Library have audiovisual material? What kinds?

Yes. The Marion E. Kenworthy Learning Center's collection includes audiocassettes and videocassettes. The audio collection has taped symposia from annual meetings since 1976; the video collection has clinical presentations useful for staff and continuing medical education. The loan period is 2 weeks. Please call for charges.



What's in the Archives?

The Archives holds the records created by the APA, such as minutes, reports, correspondence, and photographs. There are a few collections of papers of individual psychiatrists such as Daniel Blain, Leo Kanner and John C. Whitehorn. Additionally, the Archives is the sole repository for the papers of Albert Deutch. There are tapes and transcripts from an oral history project, and a collection of artifacts and photographs that relate to the history of American psychiatry. These materials may be used in the Archives or photocopied, but they do not circulate.



Does the Library have a rare book collection?

Yes. Our rare book collection contains many valuable and first editions of early works that reflect the history of psychiatry. Among its volumes are first edition copies of Benjamin Rush's *Medical Inquiries and Observations Upon the Diseases of the Mind* and Joseph Breuer and Sigmund Freud's *Studien über Hysterie*.

The growth of this collection depends on gifts. However, the Library is not authorized to give appraisals for income tax purposes.

Would you like me to donate my books and old journals to the Library?

Yes. We are always pleased to receive gifts, but we must reserve the right to evaluate your gift for relevance to the Association and dispose of any books or journals we cannot use. Each donor is appropriately acknowledged on a bookplate attached to the volume.

Would the Library like a copy of my new book?

Absolutely! In fact the APA Library began in 1961 with a collection of autographed books by member-authors. This is a tradition we especially like to keep alive.

Address:
APA Library
1400 K Street, N.W.
Washington, D.C. 20005



Phone Numbers (Area Code 202):
Archives 682-6059
Audiovisuals 682-6058
Circulation 682-6080
Computer Searches 682-6057
Reference 682-6058



No Surprises



Predictable
Rapid acting
Smooth tapering effect
Versatile
Proven safety
Unsurpassed efficacy

You've known it all along

VALIUM[®]
brand of
diazepam/Roche[®]

The cut out "V" design is a registered trademark of Roche Products Inc.

Specify "Dispense as written"



2-mg

5-mg

10-mg

scored tablets

As with any anxiolytic, patients should be cautioned against driving, operating machinery and the simultaneous ingestion of alcohol or other CNS depressant drugs.

ROCHE Roche Products

Copyright © 1989 by Roche Products Inc. All rights reserved.
Please see a summary of product information on adjacent page.

VALIUM® (diazepam/Roche) (C)

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATED: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

WARNINGS: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

PRECAUTIONS: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is

VALIUM® (diazepam/Roche)

unclear. Inform patients to consult physician before increasing dose or abruptly discontinuing diazepam.

SIDE EFFECTS: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of diazepam; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

DOSAGE: Individualize for maximum beneficial effect. **Adults:** Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. In first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) **Children:** 1 to 2½ mg t.i.d. or q.i.d. Initially, increasing as needed and tolerated (not for use under 6 months).

HOW SUPPLIED: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500. Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10.

Imprint on tablets:

2 mg—2 VALIUM® (front)
ROCHE (scored side)



5 mg—5 VALIUM® (front)
ROCHE (scored side)



10 mg—10 VALIUM® (front)
ROCHE (scored side)



ROCHE Roche Products

Roche Products Inc.
Nutley, New Jersey 07110

P.I. 0788

• POSITION AVAILABLE •

Director, Division of Basic Research
National Institute on Alcohol Abuse and Alcoholism
Alcohol, Drug Abuse, and Mental Health Administration
Public Health Service • Department of Health and Human Services

The Alcohol, Drug Abuse, and Mental Health Administration invites nominations and applications for the position of Director, Division of Basic Research.

This is a Senior Executive Service position in the career civil service, with an annual salary range of \$68,700 to \$74,900. Physicians may also be eligible for a Physician's Comparability Allowance of up to \$20,000 per year. The position is located in the National Institute on Alcohol Abuse and Alcoholism, Rockville, Maryland.

The Director, Division of Basic Research, plans and administers programs of basic research on the causes and diagnosis of alcohol abuse and alcoholism, including research in the neurosciences, biological, biochemical, behavioral, and pharmacological sciences primarily using research grants to medical schools, universities, and private organizations. The Director is responsible for the development of program plans and the formulation of budget requests, and reviews and approves program plans and justifications for each of the Branches and programs within the Division of Basic Research. The Director is responsible for the implementation of Institute policies within the Division and nationwide as they affect the research programs of the Division.

Minimum qualifications requirements include the following: a degree of Doctor of Medicine, Doctor of Osteopathy, or a bachelor's or higher degree in an academic field related to the health sciences pertinent to the work of the position. In addition, candidates should possess progres-

sively responsible experience in the scientific administration of basic research. Professional background and/or education must also include an extensive knowledge of research methodology, and a knowledge of one or more scientific disciplines that are relevant to research on alcohol abuse and alcoholism. Candidates must possess experience in the management of programs, demonstrating competence to assume leadership in planning, staffing, directing, coordinating and allocating resources, and other responsibilities associated with executive leadership of a major national program. All candidates must have had responsible professional experience at the senior level (GS-15 or equivalent).

Further information about the position and qualifications may be obtained by contacting Ms. Leslie Everheart at (301) 443-5030. Applications (Application for Federal Employment, SF 171) accompanied by a current curriculum vitae and bibliography should be submitted to Ms. Everheart at the Division of Personnel Management, Alcohol, Drug Abuse, and Mental Health Administration, 5600 Fishers Lane, Room 15C26, Rockville, Maryland 20857. Complete application material (including the SF 171) must be postmarked by July 21, 1989.

Applications from women and minority group members are especially solicited.


The Alcohol, Drug Abuse, and Mental Health Administration is an Equal Opportunity Employer.



*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.



*Antidepressant effectiveness
with once-a-day dosing**

SINEQUAN[®]

(doxepin HCl) 150-mg,† 100-mg, 75-mg, 50-mg,
25-mg, and 10-mg CAPSULES and
ORAL CONCENTRATE, 10-mg/ml,
120-ml (4-oz) bottles

Restores life's true colors

ROERIG **Pfizer**

A division of Pfizer Pharmaceuticals

SINEQUAN® (doxepin HCl)

BRIEF SUMMARY

SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

ROERIG 

A division of Pfizer Pharmaceuticals
New York, New York 10017

41st Institute on H&CP

41st Institute on H&CP

41st Institute on H&CP

41st Institute on H&CP

41st Institute on H&CP

American Psychiatric Association

Philadelphia, Pennsylvania

Adams Mark Hotel

October 15-19, 1989

Please include me on the Institute's mailing list. Return to
**Sandra Hass, Dept. 189, APA, 1400 K Street, N.W., Wash-
ington, D.C. 20005 (202) 682-6174.**

Name

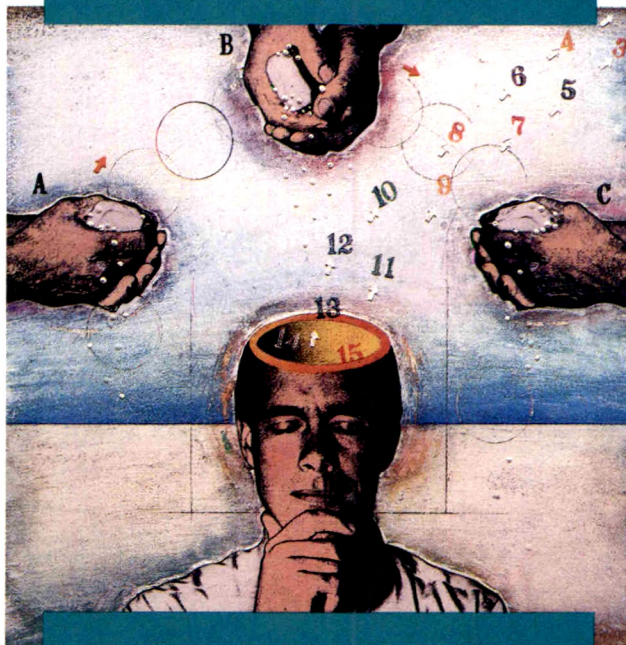
Address

City State Zip Code

41st Institute on H&CP

41st Institute on H&CP

CIBA-GEIGY ANNOUNCES



A treatment IND (investigational new drug) program for patients with Obsessive- Compulsive Disorder

FDA procedures now bring promising investigational drugs to patients earlier in the development process.

The Food and Drug Administration has established procedures to allow use of "...promising drugs for treatment of patients with serious or life-threatening illnesses..."¹ as early in the drug development process as possible and before general marketing has begun.

This OCD medication is the first psychotropic drug authorized under these new procedures.

In releasing the drug for treatment use, the FDA explained that "...studies aimed at U.S. approval... have shown sufficient evidence of effectiveness for the drug to permit its limited distribution."²

Ready supply of drug available through enrolled psychiatrists for eligible patients.

The treatment medication is being distributed by CIBA-GEIGY free of charge to psychiatrists enrolled in the treatment IND program, who will, in turn, supply the drug to eligible patients.

Patient enrollment criteria established.

Patients must be between 10 and 70 years of age, with OCD symptoms of at least one year's duration that interfere significantly with daily functioning.

For information and enrollment kits call
1-800-842-2422
between 9AM-5PM Eastern Time

¹ Young FE, Benson JS, Nightingale SL, et al: Drugs available under treatment IND. *FDA Drug Bulletin* 1988;18:14-15.

² FDA Press Release, June 6, 1988.

Announced by
CIBA-GEIGY
Pharmaceuticals
Summit, New Jersey 07901

STAFF PSYCHIATRIST

Comprehensive Mental Health Center is seeking staff psychiatrist to provide a wide range of services, including medical evaluation, psychotherapy, clinical supervision, and staff development.

Must be board certified or board eligible. Must have an Indiana license.

Competitive salary and fringe benefit program offered.

Send letter of application and vitae to:

LaNita M. James
Human Resources Department
Gary Community Mental Health Center, Inc.
1100 West 6th Avenue
Gary, Indiana 46402
(219) 885-4264

EOE/M/F



**GARY COMMUNITY
MENTAL HEALTH
CENTER INC.**

PSYCHIATRISTS

BOSTON

Fulltime and parttime psychiatrists sought for exciting mix of public and private practice. Academic appointment at the Boston University Medical Center for qualified applicants, opportunity for research and private practice and inpatient/ambulatory care at public mental health facility. Opportunity to be part of a growing group practice with ownership of stock available. A non-profit low overhead research institute is affiliated with the practice to accept grants for physicians. Superb compensation package includes fringe benefits tailored to individual needs. Minority and Spanish-speaking physicians especially sought.

Send CV in confidence to:

Richard Pillard, M.D.
Boston Psychiatric Group, P.C.
Room 905 JP
85 E. Newton St.
Boston, MA 02118.

An Affirmative Action Employer.

CHARTER HOSPITAL OF FORT WORTH

is seeking

- Board Certified Psychiatrists to work with adult and adolescent populations.
- Charter Hospital of Fort Worth is an 80 bed acute care psychiatric and chemical dependency hospital located in the southwest portion of the metroplex. Our programs cater to both adult and adolescent needs with the primary objective being that of quality patient care by superior physicians and professional staff.
- Successful candidates should be familiar with the program model of treatment and possess a strong team orientation. This is an excellent opportunity for the enthusiastic psychiatrist wishing to establish an independent and/or joint practice within a superb location. Assistance with relocation and start-up for the right person.
- Physicians interested in this expanding Fort Worth market should send resume in confidence to Special Projects Manager, Charter Hospital of Fort Worth, 6201 Overton Ridge Blvd., Fort Worth, Texas 76132.

A member of the Charter Medical Corporation family of quality health care facilities.

U.S. Public Health Service Epidemiology Training Program

Applications are being accepted for the 1990 U.S. Public Health Service (PHS) Epidemiology Training Program. **APPLICATIONS ARE DUE SEPTEMBER 1, 1989.** Training will begin approximately July 1, 1990.

Features:

The first year, trainees attend a university to study epidemiology, biostatistics, and related subjects. The subsequent two years, they will perform research with senior epidemiologists at one of the following: National Institutes of Health (NIH), Food and Drug Administration (FDA), National Center for Health Statistics (NCHS), or Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). First year salaries are currently \$32,000 for physicians and \$24,000 for non-physicians, with an increase in salary of \$2,000 each year. Educational costs and allowable relocation expenses for the first year are provided.

Eligibility:

M.D., D.O., Doctorate in an allied health profession, or Ph.D., in a biomedical or behavioral science or equivalent, and one year of postdoctoral training or experience by July 1, 1990; U.S. citizenship as of September 1, 1989; acceptability to an accredited university offering an MPH or equivalent, or more advanced public health degree.

To obtain an application and more details, send your name and home mailing address to: **NIH Training Center, PHS Epidemiology Training Program, 9000 Rockville Pike, Building 31/B2C31, Bethesda, MD 20892.**

POSITION AVAILABLE

Staff Psychiatrist, Board Eligible or Certified, for acute inpatient psychiatry unit.

This 850 bed Veterans Administration General Hospital is affiliated with the Medical College of Wisconsin. Faculty appointment is available to qualified applicants to participate in an active teaching program which includes supervision of medical students and residents.

The Psychiatric Service has a full range of psychiatric programs which includes: two 30-bed acute psychiatric units, 38-bed alcohol/drug detoxification & rehabilitation unit, outpatient psychiatry department, psychosomatics consultation-liaison service, and day treatment center. Excellent supporting staff with multidisciplinary team approach. General medical support is available in all specialties with a professionally stimulated atmosphere and multiple CME opportunities.

Metropolitan Milwaukee is a city with more than a million population, located on Lake Michigan, 80 miles north of Chicago. There are many smaller lakes surrounding the city of Milwaukee with a wide range of recreational opportunities such as sailing, boating, fishing, skiing, canoeing, hiking and hunting. Milwaukee has a large medical school, two universities (Marquette and UW-Milwaukee) and five colleges, Performing Arts Center, Milwaukee Symphony Orchestra, Florentine Opera, Repertory Theater, Conservatory of Music and the ever famous Summerfest and ethnic festivals held throughout the summer months on the lakefront.

Salary dependent on qualifications ranging from \$75,000-\$85,000 plus fringe benefits.

Interested applicants notify Dr. Nicholas Destounis, Chief of Psychiatry, Zablocki VA Medical Center, Milwaukee, Wisconsin 53295, Telephone: (414) 384-2000 #1275

CHAIR, DEPARTMENT OF PSYCHIATRY AND BIOBEHAVIORAL SCIENCE DIRECTOR, NEUROPSYCHIATRIC INSTITUTE UCLA SCHOOL OF MEDICINE

The UCLA School of Medicine is recruiting a Chair for its Department of Psychiatry and Biobehavioral Sciences who will also serve as Director of the Neuropsychiatric Institute. He/she will direct educational and patient care programs while providing leadership in the development of new research initiatives in psychiatry and the neurosciences.

Candidates are requested to submit a curriculum vitae to William N. Valentine, M.D., Chairman, Search Committee, Office of the Dean, 12-138 CHS, UCLA School of Medicine, Los Angeles, CA 90024-1722.



UCLA is an equal opportunity/affirmative action employer.

How to live with someone who's living with cancer.

When one person gets cancer, everyone in the family suffers.

Nobody knows better than we do how much help and understanding is needed. That's why our service and rehabilitation programs emphasize the whole family, not just the cancer patient.

Among our regular services we provide information and guidance to patients and families, transport patients to and from treatment, supply home care items and assist patients in their return to everyday life.

Life is what concerns us. The life of cancer patients. The lives of their families. So you can see we are even more than the research organization we are so well known to be.

No one faces cancer alone.

AMERICAN CANCER SOCIETY

PSYCHIATRIST

Swope Parkway Health Center has an immediate opening for a full-time/part-time psychiatrist. Must be board-certified or board-eligible. Must be licensed in Missouri.

Swope Parkway Health Center is JCAHO-accredited, ambulatory health center and a community mental health center providing a wide range of mental health services including:

- outpatient
- drug and alcohol
- partial hospital
- children's services
- residential care
- various preventive programs

In addition, the Health Center provides services in pediatrics, internal medicine, OB/GYN, podiatry, dental, and optometry services. Hospital privileges in two area hospitals. Center provides malpractice, CME, health/life insurance, pension, disability, holidays, and competitive salary.

Send curriculum vitae to:

Cheryl Kelow
Personnel Director
Swope Parkway Health Center
4900 Swope Parkway
Kansas City, MO 64130
(816) 923-4545, ext. 225

ADULT PSYCHIATRIST

Outstanding career opportunity to join a multidisciplinary department of psychiatry at Dean Medical Center, a multispecialty group of 200 physicians in Madison, Wisconsin. Excellent diagnostic skills as well as a thorough knowledge of psychopharmacology and psychodynamics required. Candidates with an interest in tertiary care and state of the art practice of psychiatry are especially sought.

A generous salary and comprehensive benefit program which leads to partnership in two years.

Send inquiries and resume to:

Louis C. Bernhardt, M.D.
Chairman, Recruiting Committee
Dean Medical Center
1313 Fish Hatchery Road
Madison, WI 53715

DIRECTOR PSYCHIATRIC UNIT NORTHEASTERN UNITED STATES

LOCATION: The community sits on the St. Lawrence Seaway in New York above the Thousand Islands—one hour from Ottawa and two hours from Montreal—easy access to great shopping and cultural activities. Five colleges nearby. Excellent local school system. Boating, sailing, fishing, skiing, camping and hiking are readily available. Weather is reasonable, community is above the snowbelt in New York State.

PRACTICE: Progressive community has received C.O.N. approval for a 28 bed adult psychiatric unit. Seeking Director to develop and coordinate standards of care and clinical treatment programs. Salary \$115,000+, malpractice, health insurance, etc. Relocation and visit expenses included.

For further information, send C.V. in confidence to:

Ms. Corinne I. Owens
Owens & Associates
2 Townsend St., #2-300
San Francisco, CA 94107

INDEX TO ADVERTISERS

JUNE 1989

The publication of an advertisement in this journal does not imply endorsement of the product or service by the American Psychiatric Association.

BOLAR FLUPHENAZINEA21

CIBA-GEIGY PHARMACEUTICALS
Treatment INDA47

CURRENT SCIENCEA35

DISTA PRODUCTS/DIV. OF ELI LILLY & CO.
ProzacA26-A28

DORSEY DIVISION/SANDOZ PHARMACEUTICALS
MellarilA36
PamelorA19-A20

EINSTEIN MEDICAL/PHILADELPHIA
PSYCHIATRIC CENTERA37, A39

ELCOTA33

EMPLOYMENT OPPORTUNITIESA43, A48-A50

INSTITUTE OF LIVINGA16

LEDERLE LABORATORIES
AsendinA33-A34

MCNEIL PHARMACEUTICAL
Haldol DecanoateA13-A14, C3-C4

MEAD JOHNSON PHARMACEUTICAL
BusparC2-A1
DesyrelA2

MECTA CORPORATIONA32

MERRELL DOW PHARMACEUTICALS
NorpraminA9-A10

PSYCHIATRIC INSTITUTES OF AMERICAA15

ROCHE LABORATORIES
ValiumA42-A43

ROERIG DIV./PFIZER, INC.
NavaneA6-A8
SinequanA43-A46

ST. FRANCIS HOMESA17

SMITH, KLINE, FRENCH LABS.
StelazineA31-A32

WYETH-AYERST LABORATORIES
Ativan Injection IMA22-A24

THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 146, Number 7 July 1989

In this issue:

Statutory Approaches to Limiting Psychiatrists' Liability
for Their Patients' Violent Acts

By Paul S. Appelbaum, Howard Zonana, Richard Bonnie, et al.

Seasonality and Affective Illness

By Thomas A. Wehr and Norman E. Rosenthal

Alternatives to Lithium for Preventive Treatment of Bipolar Disorder

By Robert F. Prien and Alan J. Gelenberg

Official Journal of the American Psychiatric Association

IN A WORLD WHERE CERTAINTIES ARE FEW...



Prompt clearance

Simple one-step metabolism

Predictable relief of anxiety

Dependable results

NO WONDER
Ativan[®]
(lorazepam)[®]

IS PRESCRIBED BY SO MANY
CARING CLINICIANS.

Indicate one of the following on your prescriptions, as appropriate to your state laws:

- | | |
|------------------------------------|----------------------|
| ■ Do not substitute | ■ Brand necessary |
| ■ Dispense as written | ■ May not substitute |
| ■ Medically necessary | ■ No substitution |
| ■ NDPS (no drug product selection) | |

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any anti-anxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chloridiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.



The appearances of Ativan tablets are registered trademarks of Wyeth-Ayerst Laboratories.

**WYETH-AYERST
LABORATORIES**
Philadelphia, PA 19101

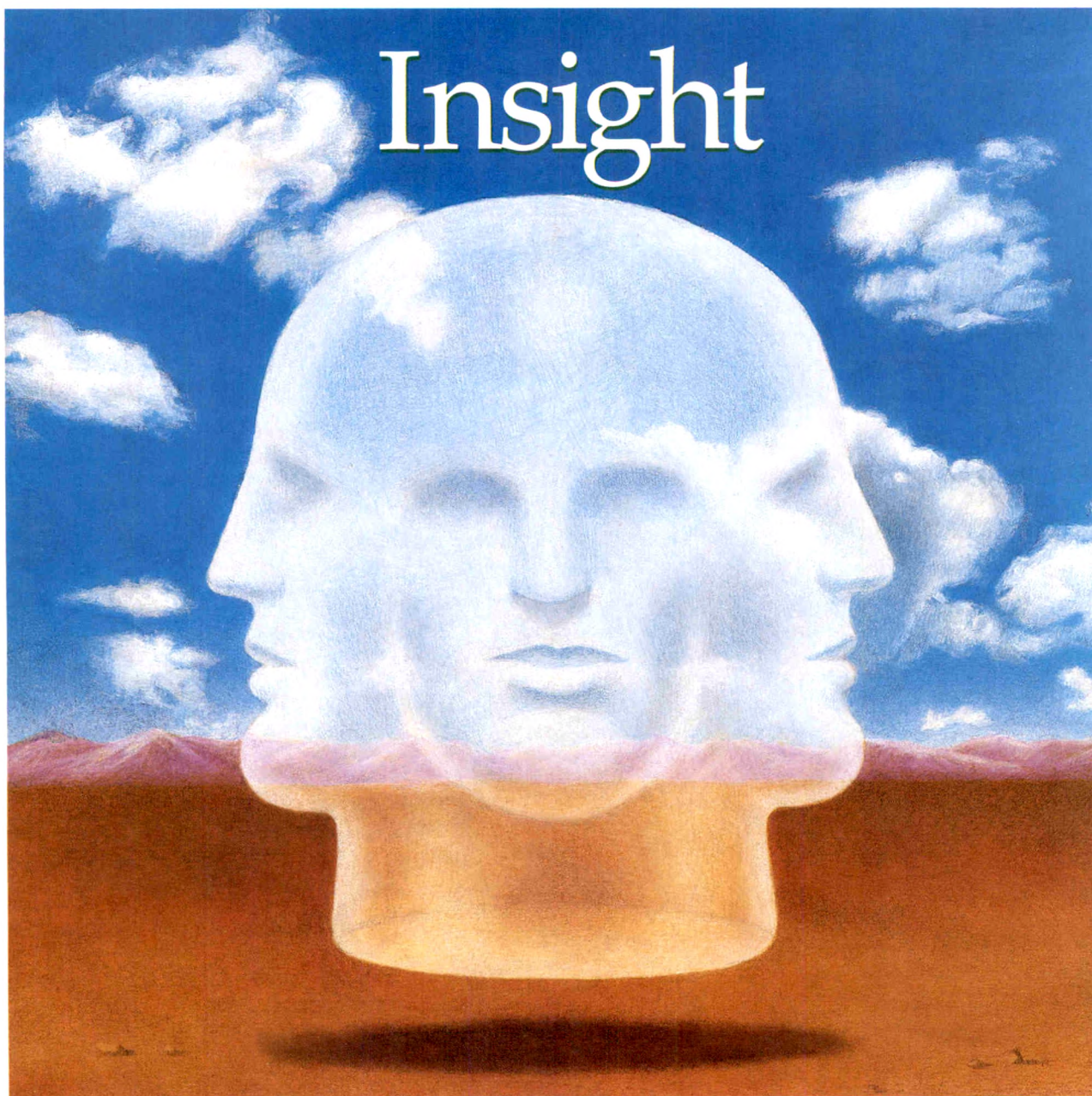
© 1989, Wyeth-Ayerst Laboratories

IN A WORLD
WHERE CERTAINTIES
ARE FEW...



NO WONDER
Ativan[®]
(lorazepam)[®]
IS PRESCRIBED BY SO MANY
CARING CLINICIANS.

Please see adjoining page for brief summary of prescribing information.



Insight. *The ability to see and understand the inner nature of things.*

Psychiatric Diagnostic Laboratories of America (PDLA®), was founded by psychiatrists for psychiatrists to help them gain greater insight into patients' needs. With over a decade of experience in providing fast, accurate results, PDLA is committed to maintaining a leadership role in the development of new diagnostic technologies.

Two recent examples of this commitment are PDLA's development of saliva tests that

eliminate the need to draw blood from difficult patients, children and the elderly.

PDLA Cortitest™ offers an excellent, non-invasive alternative to the dexamethasone suppression test, enabling the physician to determine if a patient's depression is biological in nature.

PDLA's new Saliva Lithium test offers an excellent, non-invasive alternative to monitoring patients who are on long-term lithium therapy.

To find out more about PDLA's ability to enhance your

insight, call **1-800-237-PDLA** for complete laboratory capabilities information.



**PSYCHIATRIC
DIAGNOSTIC
LABORATORIES OF
AMERICA**

100 Corporate Court
South Plainfield, NJ 07080



THE AMERICAN JOURNAL OF PSYCHIATRY

EDITOR

John C. Nemiah, M.D.

DEPUTY EDITOR

Morris A. Lipton, Ph.D., M.D.

BOOK FORUM EDITOR

Nancy C. Andreasen, M.D., Ph.D.

EDITORIAL STAFF

Managing Editor
Melanie M. Shipley
Assistant Managing Editor
Linda A. Loy
Senior Assistant Editors
Marianne K. Guerra
Laura M. Little
Jane Weaver
Assistant Editor
Marjorie M. Henry
Production Editor
Beverly M. Sullivan
Administrative Assistant
Cynthia A. Dispenza
Editorial Secretaries
Crystal DuBose
Jennifer DuPree

ASSOCIATE EDITORS

Hagop S. Akiskal, M.D.
Jonathan F. Borus, M.D.
Paula J. Clayton, M.D.
Arnold M. Cooper, M.D.
Kenneth L. Davis, M.D.
Howard H. Goldman, M.D.
Lewis L. Judd, M.D.
Toksoz Byram Karasu, M.D.
David J. Kupfer, M.D.
Judith L. Rapoport, M.D.
Loren H. Roth, M.D., M.P.H.
Charles E. Wells, M.D.
Richard Jed Wyatt, M.D.

STATISTICAL EDITORS

John J. Bartko, Ph.D.
Lee Gurel, Ph.D.

FORMER EDITORS

Amariah Brigham, M.D.
1844-1849
T. Romeyn Beck, M.D.
1849-1854
John P. Gray, M.D.
1854-1886
G. Alder Blumer, M.D.
1886-1894
Richard Dewey, M.D.
1894-1897
Henry M. Hurd, M.D.
1897-1904
Edward N. Brush, M.D.
1904-1931
Clarence B. Farrar, M.D.
1931-1965
Francis J. Braceland, M.D.
1965-1978

The American Journal of Psychiatry, ISSN 0002-953X, is published monthly by the American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005. Subscriptions: U.S. \$56.00 (student \$28.00) per year, Canada and foreign \$71.00 (student \$43.00); single issues: U.S. \$7.00, Canada and foreign \$8.00.

Business communications, changes of address, and questions about subscriptions from APA members should be directed to the Division of Member Services: (202) 682-6090. Communications from nonmember subscribers should be directed to the Circulation Department: (202) 682-6158. Authors who wish to contact the *Journal* editorial office should call (202) 682-6020.

Business Management: Nancy Frey, Director, Periodicals Services; Laura G. Abedi, Advertising Production Manager: (202) 682-6154; Beth Prester, Director, Circulation; Karen Loper, Promotion Manager; Jackie Coleman, Fulfillment Manager.

Advertising Sales: Raymond J. Purkis, Director, 2444 Morris Avenue, Union, NJ 07083; (201) 964-3100. Steve Jones, APA, 1400 K St., N.W., Washington, DC 20005; (202) 682-6329.

Type set by Byrd Data Imaging Group, Richmond, VA. Printed by The William Byrd Press, Inc., Richmond, VA.

Second-class postage paid at Washington, DC, and additional mailing offices. POSTMASTER: Send address changes to *The American Journal of Psychiatry*, Circulation Department, American Psychiatric Association, 1400 K St., N.W., Washington, DC 20005.

Indexed in *Abstracts for Social Workers*, *Biological Abstracts*, *Chemical Abstracts*, *Chicago Psychoanalytic Literature Index*, *Cumulative Index to Nursing Literature*, *Excerpta Medica*, *Hospital Literature Index*, *Index Medicus*, *International Nursing Index*, *Nutrition Abstracts*, *Psychological Abstracts*, *Science Citation Index*, and *Social Sciences Index*.

The American Psychiatric Association does not hold itself responsible for statements made in its publications by contributors or advertisers. Unless so stated, material in the *Journal* does not reflect the endorsement, official attitude, or position of the American Psychiatric Association or of the *Journal's* Editorial Board.

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by APA for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of \$00.75 per copy is paid directly to CCC, 21 Congress St., Salem, MA 01970. 0002-953X/89/\$00.75.

This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. APA does not require that permission be obtained for the photocopying of isolated articles for nonprofit classroom or library reserve use; all fees associated with such permission are waived.

Copyright © 1989 American Psychiatric Association.

THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 146, Number 7 July 1989

- | | | |
|------------------|-----|---|
| EDITORIAL | 819 | More Laws for Better Medicine? <i>Pierre Gagné</i> |
| SPECIAL ARTICLES | 821 | Statutory Approaches to Limiting Psychiatrists' Liability for Their Patients' Violent Acts <i>Paul S. Appelbaum, Howard Zonana, Richard Bonnie, and Loren H. Roth</i> |
| | 829 | Seasonality and Affective Illness <i>Thomas A. Wehr and Norman E. Rosenthal</i> |
| | 840 | Alternatives to Lithium for Preventive Treatment of Bipolar Disorder <i>Robert F. Prien and Alan J. Gelenberg</i> |
| REGULAR ARTICLES | 849 | Neurological Impairment in Violent Schizophrenic Inpatients <i>Menahem I. Krakowski, Antonio Convit, Judith Jaeger, Shang Lin, and Jan Volavka</i> |
| | 854 | Symptoms and Treatment Responses of Generalized Anxiety Disorder Patients With High Versus Low Levels of Cardiovascular Complaints <i>Rudolf Hoehn-Saric, Daniel R. McLeod, and Wesley D. Zimmerli</i> |
| | 860 | Relapse and Rebound Following Discontinuation of Benzodiazepine Treatment of Panic Attacks: Alprazolam Versus Diazepam <i>Peter P. Roy-Byrne, Stephen R. Dager, Deborah S. Cowley, Peter Vitaliano, and David L. Dunner</i> |
| | 866 | Startle Modulation in Children With Posttraumatic Stress Disorder <i>Edward M. Ornitz and Robert S. Pynoos</i> |
| | 871 | Developmental Perspectives in Child and Adolescent Depressive Symptoms in a Community Sample <i>Javad H. Kashani, Tomas K. Rosenberg, and John C. Reid</i> |
| | 876 | Psychosocial Distress and Well-Being Among Gay and Bisexual Men With Human Immunodeficiency Virus Infection <i>Henry T. Chuang, Gerald M. Devins, John Hunsley, and M. John Gill</i> |
| | 881 | Private and Public Psychiatry: A Comparison of Two Health Care Systems <i>Gavin Andrews</i> |
| | 887 | The Presumptive Role of Fantasy in Serial Sexual Homicide <i>Robert Alan Prentky, Ann Wolbert Burgess, Frances Rokous, Austin Lee, Carol Hartman, Robert Ressler, and John Douglas</i> |
| COMMENTARY | 892 | Late Luteal Phase Dysphoric Disorder and DSM-III-R <i>Robert L. Spitzer, Sally K. Severino, Janet B.W. Williams, and Barbara L. Parry</i> |

**BRIEF
COMMUNICATIONS**

- 898 Effect of a Psychiatric Liaison Program on Consultation Rates and on Detection of Minor Psychiatric Disorders in Cancer Patients
Cheryl F. McCartney, Patricia Cahill, David B. Larson, John S. Lyons, Cecilia Y. Wada, and Harold Alan Pincus
- 902 Informed Consent and Tardive Dyskinesia *Irwin Kleinman, Debbie Schachter, and Endre Koritar*
- 905 Dopamine Blockade and Clinical Response: Evidence for Two Biological Subgroups of Schizophrenia *Adam Wolkin, Faouzia Barouche, Alfred P. Wolf, John Rotrosen, Joanna S. Fowler, Chyng-Yann Shiue, Thomas B. Cooper, and Jonathan D. Brodie*

**CLINICAL AND
RESEARCH REPORTS**

- 909 Open Trial of Fluoxetine in Obsessive-Compulsive Disorder
Michael A. Jenike, Lynn Buttolph, Lee Baer, Joseph Ricciardi, and Amy Holland
- 911 Elevated Antidepressant Plasma Levels After Addition of Fluoxetine
Robert B. Aranow, James I. Hudson, Harrison G. Pope, Jr., Tana A. Grady, Thomas A. Laage, Iris R. Bell, and Jonathan O. Cole
- 914 Adjunctive Buspirone in Benzodiazepine Treatment of Four Patients With Panic Disorder *David R. Gastfriend and Jerrold F. Rosenbaum*
- 917 Plasma Lipid Levels in Patients With Panic Disorder or Agoraphobia
Chris Hayward, C. Barr Taylor, Walton T. Roth, Roy King, and W. Stewart Agras
- 920 Late-Life Onset of Panic Disorder With Agoraphobia in Three Patients
Daniel J. Luchins and Robert P. Rose
- 922 Three Cases of Panic Disorder With Agoraphobia in Children
James C. Ballenger, Donald J. Carek, Jane J. Steele, and Denise Cornish-McTighe
- 925 Midazolam for Aggressivity and Violence in Three Mentally Retarded Patients *William S. Bond, Laura A. Mandos, and Michael B. Kurtz*

BOOK FORUM

927

**LETTERS
TO THE EDITOR**

939

- 950 Correction: Patrick E. Ciccone: "Refinement of the Diagnosis of Schizophreniform Disorder" (letter) (1989; 146:561-562)

OTHER

- 886 Deceased Members of the American Psychiatric Association
- A10 Officers of the American Psychiatric Association
- A16 Calendar
- A35 *British Journal of Psychiatry* Contents (May 1989)
- A40 Index to Advertisers
- A41 Information for Contributors
- A46 *Psychological Medicine* Contents (May 1989)

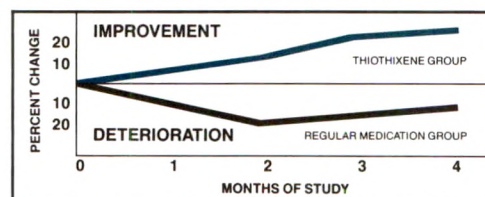


"IT FEELS GOOD TO FEEL USEFUL AGAIN"

For the chronic schizophrenic patient, Navane can mean more competent work performance,^{1,2} and a smoother path towards social recovery. Navane may help improve the ability to concentrate, and promote a better attitude toward work and co-workers.¹⁻³

Anticholinergic⁴ and cardiovascular^{5,6} side effects in patients treated with Navane are reported infrequently. Should extrapyramidal symptoms occur, they usually can be controlled.

**27% rise in work output
compared to baseline shown
in patients switched to Navane^{2,3}**

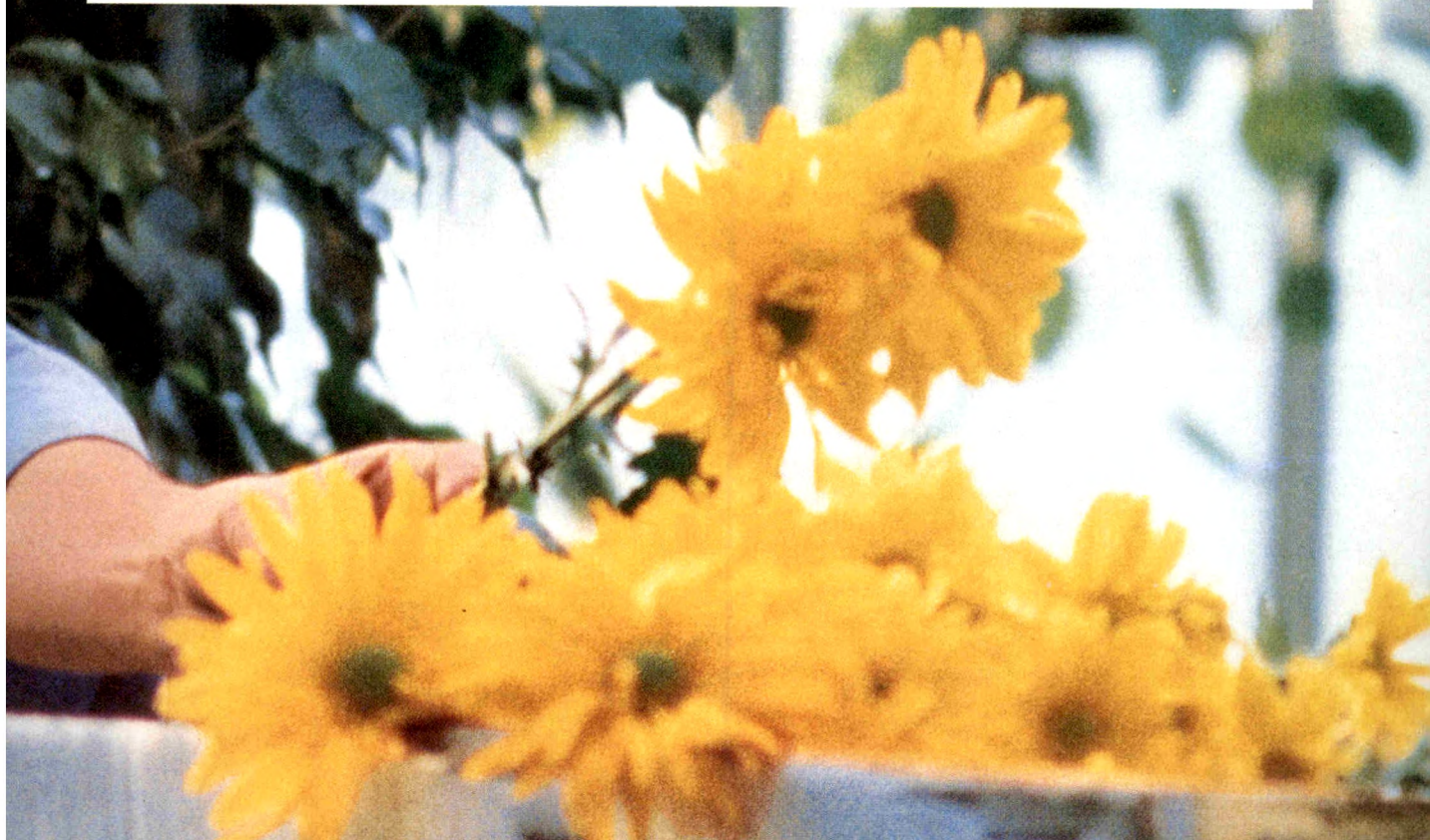


(Adapted from DiMascio and Demigian^{2,3})

Forty-two psychotic male and female patients under age 55 were entered in this study on a nonblind basis, and randomly assigned to their regular medication or switched to thiothixene. Patients were evaluated at baseline and on a daily basis, and periodically rated on the Global Improvement and Brief Psychiatric Rating Scales.

In schizophrenia,
Navane[®] (thiothixene)(thiothixene HCl)

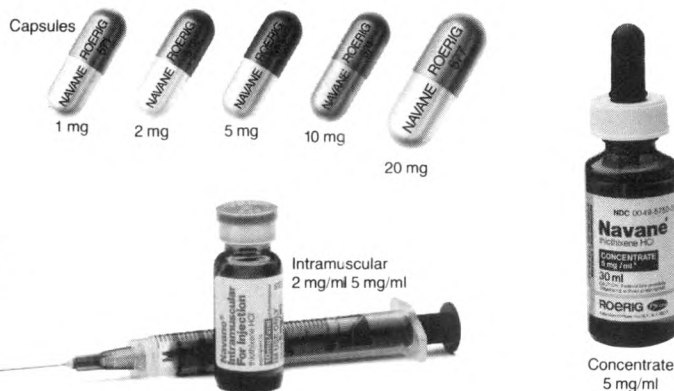
Please see brief summary of NAVANE[®] (thiothixene/thiothixene HCl) prescribing information on adjacent page.



Navane®

(thiothixene) (thiothixene HCl)

It feels good to feel useful again



References: 1. Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2. DiMascio A, Demigian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3. DiMascio A, Demigian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association, Washington, DC, May 3-6, 1971. 4. Goldstein B, Weiner D, Baner J: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients. In Lehmann HE, Ban JA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry*. Basel, Switzerland, S. Karger, 1969, vol 2, pp 45-52. 5. Dillenkoff RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of the American Psychiatric Association, Dallas, May 1-4, 1972. 6. Data available on request from Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg

(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.

Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility it should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged

periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmic involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecostasia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

ROERIG Pfizer

A division of Pfizer Pharmaceuticals
New York, New York 10017

FREUD

by

Anthony Storr

Sigmund Freud developed a totally new way of looking at human nature. Only now, with the hindsight of the half-century since his death, can we assess his true legacy to twentieth-century thinking. In this new addition to the highly-acclaimed *Past Masters* series, Anthony Storr—experienced psychiatrist and author of *Solitude*—does just that, offering a clear and objective look at Freud and his major theories.

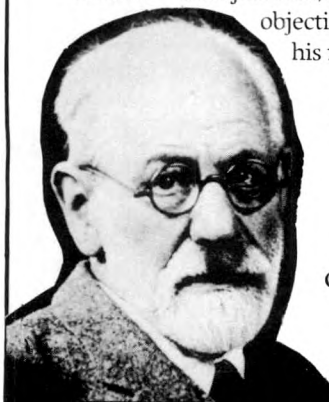
Commemorating the fiftieth anniversary of Freud's death

PAST MASTERS

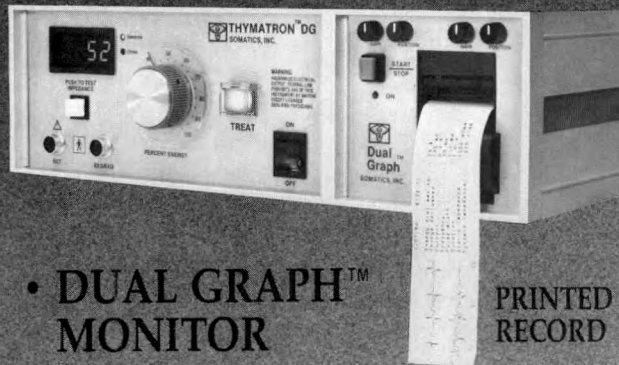
144 pp. paper \$5.95

OXFORD PAPERBACKS

Oxford University Press
200 Madison Avenue
New York, NY 10016



The New Standard for ECT THYMATRON™ DG



- DUAL GRAPH™ MONITOR
- ADJUSTABLE STIMULUS
- CHRONA™ DIGITAL TIMER

PRINTED
RECORD



SOMATICS, INC.

910 Sherwood Drive, Unit 18
Lake Bluff, IL 60044

Interstate toll-free 800-642-6761
Illinois 312-234-6761
Canada toll-free 800-343-3153

When so much depends on you . . .

THE CHILDREN'S CAMPUS

- A comprehensive residential treatment center providing a true continuum of care. **The Children's Campus** has been serving troubled children and adolescents for over 100 years
- **The Children's Campus** is designed to be more than a single focused residential facility. The Children's Campus utilizes a "Continuum of Treatment" based upon realistic expectations and needs.
- **The Children's Campus** offers a start-to-finish approach utilizing individualized applications of a variety of established treatment components, supported by a structured positive living environment.
- The fundamental goal of all **The Children's Campus** interventions is to enable the child to work through life issues and emerge as an individual with a healthy self-concept, a strong value system, and the ability to make appropriate and responsible choices.
- The "Continuum of Treatment" offered by **The Children's Campus** allows the child to move from a more restrictive environment when appropriate to a less restrictive environment, avoiding the trauma of a new setting, new treatment, and new faces.
- **The Children's Campus** is located in beautiful North Central Indiana only a few hours away from Chicago, Indianapolis, Detroit, and Cleveland. The Children's Campus is only ten minutes from the University of Notre Dame.

For more information, call or write:

Admissions Coordinator
The Children's Campus
1411 Lincoln Way West
Mishawaka, IN 46544-1690
(219) 259-5666

Third Party reimbursement accepted



CWLA



**PSYCHIATRIC &
PSYCHOLOGICAL SERVICES**

**DIAGNOSTIC AND
EVALUATION SERVICES**

**PREFERRED ADOLESCENT
CARE CENTER**

SEXUAL ABUSE TREATMENT

**SUBSTANCE ABUSE
TREATMENT**

ON-GROUNDS SCHOOL

TREATMENT GROUP HOMES

TREATMENT FOSTER HOMES

INDEPENDENT LIVING

PREGNANCY PROGRAM

**MOTHER/INFANT BONDING
PROGRAM**

FAMILY SUPPORT PROGRAM

The American Psychiatric Association

1400 K Street, N.W., Washington, D.C. 20005

OFFICERS 1988–1989

President: Herbert Pardes
President-Elect: Elissa P. Benedek
Vice-President: Lawrence Hartmann
Vice-President: Fred Gottlieb
Secretary: Philip M. Margolis
Treasurer: Alan I. Levenson

ASSEMBLY

Speaker: Gerald H. Flamm
Speaker-Elect: Edward Hanin
Recorder: Bernice B. Elkin

BOARD OF TRUSTEES

Daniel B. Borenstein
Robert J. Campbell III
Paul J. Fink
Emanuel E. Garcia
Merlin Johnson
Linda Logsdon
Eliza W. Menninger
Rodrigo A. Munoz
Pete C. Palasota
Robert O. Pasnau
Roger Peele
George H. Pollock
Herbert S. Sacks
Douglas A. Sargent
Chester W. Schmidt, Jr.

MEDICAL DIRECTOR'S OFFICE

Medical Director: Melvin Sabshin
Deputy Medical Directors: John M. Hamilton
Harold A. Pincus
Carolyn B. Robinowitz
Jeanne Spurlock

CHAIRPERSONS OF COUNCILS, COMMISSIONS, COMMITTEES, AND TASK FORCES

CONSTITUTIONAL COMMITTEES

Budget
Constitution and By-Laws
Elections
Ethics
Tellers
Membership
Nominating
Reference
Resource Development

Steven S. Sharfstein
Ralph A. O'Connell
Bernice B. Elkin
Robert J. McDevitt
Edward C. Kirby, Jr.
Michael J. Vergare
Paul J. Fink
Elissa P. Benedek
Howard F. Wallach

COUNCIL ON AGING

Nursing Homes and Elderly Mentally Ill
Education and Training in
Geriatric Psychiatry
Geriatric Psychiatry in the Public
Mental Health Sector
Ethnic Minority Elderly
White House Conference on Aging
Reimbursement for Elderly Mentally Ill

Jerome Yesavage
Benjamin Liptzin
Charles A. Shamoian
Barry Steven Fogel
Kenneth Mark Sakauye
Sanford Irwin Finkel
Howard Hirsch Goldman

COUNCIL ON CHILDREN, ADOLESCENTS, AND THEIR FAMILIES

Chronically Ill and Emotionally
Handicapped Children
Confrontational Therapies
Juvenile Justice Issues
Psychiatry and Mental Health in Schools
Family Violence and Sexual Abuse
Psychiatric Aspects of New Reproductive
Technologies

Larry B. Silver
Cynthia R. Pfeffer
Mark J. Blotcky
William M. Buzogany
Irving H. Berkovitz
Sandra J. Kaplan
Miriam B. Rosenthal

COUNCIL ON ECONOMIC AFFAIRS

Financing and Marketing
JCAH Standards for Hospital-Based,
Hospital-Related Services
Interprofessional Affairs
Social Security Income/Disability Insurance
Prospective Payment Issues
Future Trends in Private Insurance
Psychiatrist Payment
Quality Assurance

Donald J. Scherl
Robert O. Friedel
Boris M. Astrachan
Mildred Mitchell-Bateman
Arthur T. Meyerson
Joseph T. English
Robert W. Gibson
Boris M. Astrachan
George Wilson

COUNCIL ON INTERNAL ORGANIZATION

Arrangements
Scientific Program
Film
Scientific and Educational Exhibits
Video
Information Systems

Ronald A. Shellow
Kathleen Bell Unger
Mel Blaustein
Allan Tasman
Bernard Martin Morenz
Jean Patricia Goodwin
Donald Carl Fidler
Wandal W. Winn

Foundations' Fund Prize for Research in Psychiatry

Grants and Awards
Manfred S. Guttmacher Award
Marie H. Eldredge Award
Hospital and Community Psychiatry
Achievement Awards
Isaac Ray Award
Ittleson Award
Weinberg Memorial Award
McGavin Award
Vestermark Award
Samuel G. Hibbs Award
Advertising
Headquarters
Member Life, Accident, and Health
Insurance
Special Benefit Programs
Personnel
Advertisers and Exhibitors
Telemedical Services
History and Library
Exhibits Advisory
Friends of the APA
PIA Foundation Hospital Research Awards

Ira D. Glick
Alan I. Levenson
William H. Reid
Bernice E. Coleman
Doris Lee Dickens
Richard T. Rada
Dennis P. Cantwell
Sanford I. Finkel
Mina Karen Dulcan
Bryce Templeton
Steven M. Mirin
Will D. Strathmann
Raymond I. Band
Harvey Bluestone
Abram M. Hostetter
Maurice J. Martin
Henry H. Work
Jane H. Preston
Lucy D. Ozarin
Joseph H.B. Honnigford
Evelyn P. Ivey-Davis
H. Richard Lamb

COUNCIL ON INTERNATIONAL AFFAIRS

Abuse and Misuse of Psychiatry and
Psychiatrists
Inter-American Council Liaison
Human Rights
Psychosocial Aspects of the Middle
East Process
International Education
Joint Meeting in Germany in 1990

Harold M. Visotsky
Michael R. Zales
Jorge A. Costa e Silva
Lawrence Hartmann
George Tarjan
Normund Wong
Eric Plaut

COUNCIL ON MEDICAL EDUCATION AND CAREER DEVELOPMENT

Administrative Psychiatry
Medical Student Education
Graduate Education
Continuing Education
Consultation-Liaison Psychiatry and
Primary Care Education
Impaired Physician
Communication Between APA and ABPN
Recertification
Independent Study
PKSAP-VI
Residents
Post Residency Fellowship Programs

Joel Yager
Stephen L. Rachlin
Leah Joan Dickstein
Stefan P. Stein
John W. Goethe
Troy L. Thompson II
Robert W. McDermott
Richard I. Shader
Joe P. Tupin
Keith Hadley Johansen
Gordon Darrow Strauss
Henry Carl Emmons
George H. Pollock

APA/Burroughs Wellcome Fellowship	Roger Peele	Practice of Psychotherapy	Marcia Kraft Goin
APA/Mead Johnson Fellowship	James T. Barter	Practice Issues in Organized/Managed Care	Haroutun Babigian
APA/NIMH Minority Fellowship Program	Charles A. Pinderhughes	COUNCIL ON PSYCHIATRY AND LAW	Howard V. Zonana
Psychiatric Leadership in Public Mental Health Programs	Robert L. Leon	Confidentiality	Aron S. Wolf
Education Activities for DSM-III-R	Michael A. Fauman	Treatment Records in Child Custody Disputes	Carl P. Malmquist
COUNCIL ON NATIONAL AFFAIRS	Lindbergh S. Sata	Psychiatric Diagnoses in the Courts	Seymour L. Halleck
Abuse and Misuse of Psychiatry in U.S.	Roger Dale Walker	COUNCIL ON RESEARCH	John E. Adams
Asian-American Psychiatrists	Joyce S. Kobayashi	Electroconvulsive Therapy	Richard D. Weiner
Black Psychiatrists	Ernest A. Kendrick	Long-Term Effects of Lithium on Kidney	George R. Heninger
American Indian and Alaskan		Treatments of Psychiatric Disorders	T. Byram Karasu
Native Psychiatrists	Linda K. Cross	Tardive Dyskinesia	John Michael Kane
Foreign Medical Graduates	Walter Weintraub	Psychosocial Treatment Research	John P. Docherty
Religion and Psychiatry	Marc Galanter	Prevention Research	Robert M. Rose
Hispanic Psychiatrists	Eduardo R. Val	Biographical Directory	Robert Alan Dorwart
Women	Nada Logan Stotland	Benzodiazepine Dependency	Carl Salzman
Gay, Lesbian, and Bisexual Issues	James Paul Krajeski	Psychiatric Diagnosis and Assessment	Layton McCurdy
Occupational Psychiatry	Duane Q. Hagen	Research on Psychiatric Treatments	John M. Kane
Psychological Aspects of Nuclear Arms Development	Judith E. Lipton	DSM-IV	Allen J. Frances
Victimization	Martin Symonds	COMMISSION ON JUDICIAL ACTION	Paul Appelbaum
COUNCIL ON PSYCHIATRIC SERVICES	J. Frank James	CONSULTATION SERVICE BOARD	Dave M. Davis
Alcoholism	Richard J. Frances	ETHICS APPEALS BOARD	Elissa P. Benedek
Clinician Safety	William R. Dubin	JOINT COMMISSION ON PUBLIC AFFAIRS	Harvey L. Ruben
Drug Abuse	Edward Kaufman	JOINT COMMISSION ON GOVERNMENT RELATIONS	John J. McGrath
Rehabilitation	Arthur T. Meyerson	SPECIAL COMPONENTS	
State Mental Health Systems	Ernest W. Klatte	Board Committee on Insurance	Alan I. Levenson
American Hospital Association	Mark A. Gould	Investment Advisory Committee	Frederick Amling
Functions of the Hospital and Community Psychiatry Service, Journal, and Institute	H. Richard Lamb	Long-Range Planning Committee	Robert O. Pasnau
Institute on Hospital and Community Psychiatry Program	Leonard I. Stein	Executive Compensation Committee	William L. Webb, Jr.
Psychiatric Services for Mentally Retarded/Developmentally Disabled Adults	Ludwik S. Szymanski	Work Group on Federal Government Organizational Structure	Daniel X. Freedman
Chronically Mentally Ill	David L. Cutler	Work Group on Codes and Reimbursement	Chester W. Schmidt, Jr.
Veterans Administration Affairs	Frederick G. Guggenheim	Commission on AIDS	Stuart E. Nichols, Jr.
Private Practice	Boris G. Rifkin		
Jails and Prisons	Henry C. Weinstein		
Psychiatric Services in the Military	Leonora K. Petty		

Coming in the August 1989 issue of

THE AMERICAN JOURNAL OF PSYCHIATRY

Psychotic Disorders in DSM-III-R

By Kenneth S. Kendler, Robert L. Spitzer, and Janet B.W. Williams

Neurochemical Abnormalities of Anorexia Nervosa and Bulimia Nervosa

By Maurizio Fava, Paul M. Copeland, Ulrich Schweiger, et al.

Psychiatric Aspects of Organ Transplantation

By Owen S. Surman

Now, with the American Psychiatric Association Gold MasterCard®, keeping up with Continuing Medical Education requirements is easier than ever.

Through an exclusive arrangement with Physicians' Travel & Meeting Guide, one toll-free call is all it takes to get the latest information about CME meetings, seminars and conferences and make all the necessary hotel and airline reservations. Finally, a single source for CME Travel — you decide where you want to go and the American Psychiatric Association Gold MasterCard takes care of the rest.

Take the credit you deserve

Developed exclusively for physicians, this Gold MasterCard can help make any trip a pleasure. Request the American Psychiatric Association Gold MasterCard for instant access to CME events and an unmatched level of benefits and services, including:

- higher lines of credit — up to \$25,000
- issued free of an annual fee for the first year† (\$30 each year thereafter)
- Premium Buyer's Protection
- up to \$1,000,000 Travel Accidental Death and Dismemberment Insurance
- Travelers' Emergency Assistance Network
- 24-Hour Toll-Free Customer Satisfaction
- and more travel-related services than any other Gold MasterCard

To apply, complete the attached application and return it to: American Psychiatric Association Gold MasterCard, P.O. Box 15464, Wilmington, DE 19885-9440. Or, for more immediate attention or answers to your questions, call toll free: 1-800-847-7378. Be sure to reference the special code BHPE for faster service.

†16.9% Annual Percentage Rate. Certain restrictions apply to these and other benefits as described in the brochure that accompanies your Premium Access Checks.

The MBNA® Gold MasterCard®... Your Passport to CME Travel.



YES! I wish to request the American Psychiatric Association Gold MasterCard® and all the benefits described in this advertisement. I understand that my card will be issued free of an annual fee for the first year and each year thereafter the fee is \$30. I further understand that if I do not qualify for a Gold MasterCard, this constitutes my application for an American Psychiatric Association MasterCard. (Note: This is not an application for a corporate account.)

NAME _____ (PLEASE PRINT)

ADDRESS _____

CITY _____ STATE _____ ZIP _____

PREVIOUS ADDRESS _____

HOME PHONE () _____ BUSINESS PHONE () _____

Are you ☐ Renting ☐ Own ☐ Buying Monthly Payment \$ _____

SOCIAL SEC. NO. _____ DATE OF BIRTH _____

PRACTICE/EMPLOYER _____ YEARS THERE _____

ANNUAL SALARY \$ _____ OTHER INCOME \$ _____ SOURCE _____
(Alimony, child support, or separate maintenance income need not be revealed if you do not wish it considered as a basis of repayment.)

MOTHER'S MAIDEN NAME _____
(For use when you request special action taken on your account)

I have read this entire application, agree to its terms, and certify the information is correct.

X _____ (SEAL)
APPLICANT SIGNATURE _____ DATE _____

CURRENT CREDIT CARD ACCOUNTS

BHPE
04-556
01-249

My MasterCard®/VISA® Account # is: _____

If you wish an additional card issued _____ a co-applicant over 18 years of age complete the information below.

CO-APPLICANT NAME _____ Relationship _____

SOCIAL SEC. NO. _____ BUSINESS PHONE () _____

EMPLOYER _____ POSITION _____

ANNUAL SALARY \$ _____ OTHER INCOME \$ _____

(Alimony, child support, or separate maintenance income need not be revealed if you do not wish it considered as a basis of repayment.)
I have read this entire application and agree to its terms, and understand that I will be jointly and severally liable for all charges on the account.

X _____ (SEAL)
CO-APPLICANT SIGNATURE _____ DATE _____

I (We) authorize MBNA® to investigate any facts, or obtain and exchange reports regarding this application and/or resulting account with credit reporting agencies and others. Upon request I (We) will be informed of each agency's name and address.

Annual Fee(s)	\$30 Gold MasterCard, \$20 Silver MasterCard (Fee waived first year)
Annual Percentage Rate	16.9%
Grace Period For Repayment Of Balance For Purchases	At least 25 Days from statement closing date
Method of Computing the Balance for Purchases	Average Daily Balance (including new purchases)
Transaction Fee For Cash Advances, And Fees For Paying Late or Exceeding The Credit Limit	Transaction Fee For Bank and ATM Cash Advances: 2% of each Cash Advance, \$2 Minimum, \$25 Maximum. Transaction Fee For Access Check Cash Advances: 1% of each Cash Advance, \$2 Minimum, \$10 Maximum. Late Payment Fee: \$15 Over-the-Credit-Limit Fee: \$15

The information about the cost of the card described in this application is accurate as of 5/1/89. This information may have changed after that date. To find out what may have changed, call us at 1-800-847-7378.



MBNA® is a federally registered service mark of Maryland Bank N.A., an MNC Financial, Inc., company.
MasterCard® is a federally registered service mark of MasterCard International, Inc.



No Surprises



Predictable
Rapid acting
Smooth tapering effect
Versatile
Proven safety
Unsurpassed efficacy

You've known it all along

VALIUM[®]
brand of
diazepam/Roche[®]

The cut out "V" design is a registered trademark of Roche Products Inc.

Specify "Dispense as written"



As with any anxiolytic, patients should be cautioned against driving, operating machinery and the simultaneous ingestion of alcohol or other CNS depressant drugs.

VALIUM® (diazepam/Roche) (V)

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATED: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

WARNINGS: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

PRECAUTIONS: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is

VALIUM® (diazepam/Roche)

unclear. Inform patients to consult physician before increasing dose or abruptly discontinuing diazepam.

SIDE EFFECTS: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of diazepam; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

DOSAGE: Individualize for maximum beneficial effect. **Adults:**

Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) **Children:** 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

HOW SUPPLIED: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500.

Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10.

Imprint on tablets:

2 mg—2 VALIUM® (front)

ROCHE (scored side)



5 mg—5 VALIUM® (front)

ROCHE (scored side)



10 mg—10 VALIUM® (front)

ROCHE (scored side)



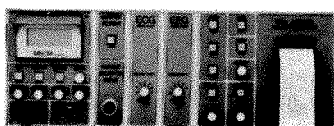
Roche Products

Roche Products Inc.
Manati, Puerto Rico 00701

P.1. 0788

INTELLIGENT ECT FROM MECTA CORP. UL LISTED CSA CERTIFIED MODULAR AND COMPUTERIZED

SR-1



JR-1



FLEXIBILITY



**PRINTED SELF TEST
AND TREATMENT RESULTS**

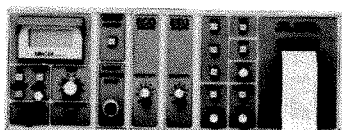
ADDITIONAL FEATURES INCLUDED WITH ALL SR MODELS ARE:

- EEG instrumentation amplifier
- Built-in 2 channel digital chart recorder
- Numeric timing marks during monitoring
- Printed record of energy level
- Printed date and time of treatment
- ECG instrumentation amplifier
- Selectable single or dual channel
- Printed record of treatment and self test
- Printed record of stimulus parameters
- Modular design for maximum flexibility

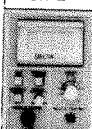
SR/JR FEATURES INCLUDE:

- Continuous reading of energy in Joules
- Tiltable Liquid Crystal Display
- Bi-polar brief pulse stimulus
- Adjustable constant current stimulus
- Audible warning prior to treatment
- Remote control capabilities
- 100% expected seizure induction
- Totally isolated for maximum safety
- Single or multiple energy control(s)
- All parameters displayed in text form
- Increased energy for difficult cases
- Built-in self test for patient safety
- Steady warning tone during treatment
- Protected STIMULUS CONTROL push button
- Timing accuracy better than .1%
- 1 year parts and labor warranty
- Operates on 120 or 240 VAC
- Complete with all accessories

SR-2



JR-2



**SINGLE ENERGY
LEVEL CONTROLS**

SIMPLICITY

MECTA Corporation 5622 SW Kelly Street Portland, OR 97201 (503) 245-6975

AUSTEN RIGGS CENTER



Psychoanalytic Psychotherapy in an
Open Hospital Setting

Treatment with Dignity, Personal
Responsibility and Quality Long-Term Results

The Austen Riggs Center
Stockbridge, Massachusetts 01262

(413) 298-5511

Founded in 1919

Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.

SEPTEMBER

September 4-7, International Medical Congress on the Detection and Examination of Human Rights Violations, Copenhagen. Contact Jette Christiansen, Medical Congress on Human Rights, c/o Amnesty International, Medical Group, Frederiksborggade 1, 1360 Copenhagen K, Denmark; 01-11-89-29.

September 5-8, 4th Congress of the International Psychogeriatric Association, Tokyo. Contact Akira Homma, M.D., Department of Psychiatry, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 213, Japan; 044-977-8111, Ext. 3200.

September 6-9, annual meeting, National Rehabilitation Association, Orlando, Florida. Contact Robert E. Brabham, Ph.D., Executive Director, 633 S. Washington Street, Alexandria, VA 22314; 703-836-0850.

September 12-15, 3rd International Congress on Ethics in Medicine, Stockholm. Contact Third International Congress on Ethics in Medicine, Beth Israel Medical Center, 1st Avenue at 16th Street, New York, NY 10003; 212-420-4082.

September 14-16, 5th International Conference of Alzheimer's Disease International, Dublin. Contact Alzheimer's Disease International, Conference Secretariat, 12 Pembroke Park, Dublin 4, Ireland.

September 15-17, annual meeting, Epilepsy Foundation of America, Memphis. Contact William M. McLin, Executive Vice-President, 4351 Garden City Drive, Suite 406, Landover, MD 20785; 301-459-3700.

September 18-21, annual meeting, American Academy of Family Physicians, Los Angeles. Contact Robert Graham, M.D., Executive Vice-President, 8880 Ward Parkway, Kansas City, MO 64114; 816-333-9700.

September 20-24, 1st European Congress of Ericksonian Hypnosis and Psychotherapy, Heidelberg, West Germany. Contact Burkhard Peter, Dipl.Psych., Milton Erickson Gesellschaft für klinische Hypnose (M.E.G.), Konradstr. 16, D-8000 München 40, West Germany; 089-2180-5175.

September 22-23, National Conference on Drug Abuse and Sport: Prevention, Intervention, Elimination, Baltimore. Contact Dr. Michael J. Asken, Chairperson, or Stephen Seitz, Coordinator, Sport Psychology Center of the Shep-

pard-Pratt Hospital System, P.O. Box 6815, Baltimore, MD 21285-6815; 1-800-627-0550.

September 23-27, 3rd Annual Conference on the Foundations of Behavioral Neurology, Stockholm. Contact Ann McCormack, Southern California Neuropsychiatric Institute, 6794 La Jolla Boulevard, La Jolla, CA 92037; 619-454-2102.

September 24-27, annual meeting, American Neurological Association, New Orleans. Contact Maura L. McCone, Assistant Executive Director, 2221 University Avenue, S.E., Suite 350, Minneapolis, MN 55414; 612-378-3290.

September 24-28, annual meeting, World Medical Association, Hong Kong. Contact Angel Orozco, Executive Director, 28, Avenue des Alpes, 01210 Ferney-Voltaire, France; 50-40-75-75.

September 26-29, annual meeting, American College of Emergency Physicians, New Orleans. Contact Colin C. Rorie, Jr., Ph.D., Executive Director, P.O. Box 619911, Dallas, TX 75261-9911; 214-550-0911.

September 28-October 1, annual meeting, American School Health Association, Orlando, Florida. Contact Dana A. Davis, Executive Director, P.O. Box 708, Kent, OH 44240; 216-678-1601.

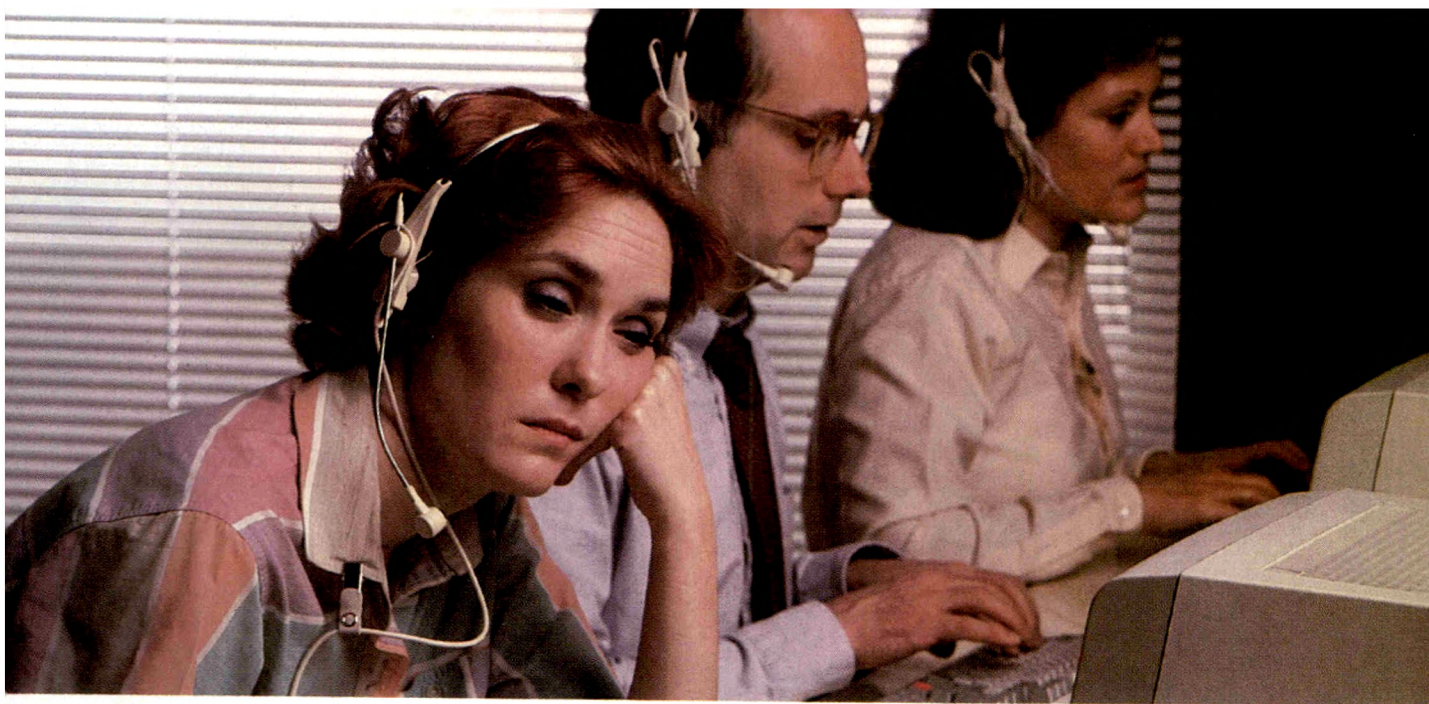
OCTOBER

October 4-8, annual meeting, Southern Psychiatric Association, Asheville, North Carolina. Contact Margo S. Adams, Executive Secretary, P.O. Box 10002, Tallahassee, FL 32302; 904-222-8404.

October 5-7, annual meeting, National Association for Retarded Citizens, San Antonio, Texas. Contact Alan Abeson, Ed.D., Executive Director, 2501 Avenue J, Arlington, TX 76006; 817-640-0204.

October 8-11, 10th World Congress, International College of Psychosomatic Medicine, Madrid. Contact Professor J.J. Lopez-Ibor, Clinica Lopez Ibor, Calle Nueva Zelanda 44, Puerta de Hierro, E-28035 Madrid, Spain.

(Continued on page A27)



Asleep at the switch. This calls for a switch in antidepressants.

With PAMELOR there is little daytime sedation.¹⁻⁶
Yet all the efficacy of amitriptyline.⁷


PAMELOR®
(nortriptyline HCl)

The active metabolite of amitriptyline

PAMELOR may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating heavy machinery or driving a car; therefore, the patient should be warned accordingly.

References: 1. Thompson TL II, Thompson WL. Treating depression: tricyclics, tetracyclics, and other options. *Modern Medicine*. August 1983;51:87-109. 2. Georgotas A. Affective disorders: pharmacotherapy. In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry IV*. Baltimore, Md: Williams & Wilkins; 1985:1821-833. 3. Bye C, Clubley M, Peck AW. Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol*. 1978;6:155-161. 4. Kupfer DJ, Spiker DG, Rossi A, Coble PA, Shaw D, Ulrich R. Nortriptyline and EEG sleep in depressed patients. *Biol Psychiatry*. 1982;17:535-546. 5. Blackwell B, Peterson GR, Kuzma RJ, Hostetler RM, Adolph AB. The effect of five tricyclic antidepressants on salivary flow and mood in healthy volunteers. *Communications in Psychopharmacol*. 1980;4:255-261. 6. Hayes PE, Kristoff CA. Adverse reactions to five new antidepressants. *Clin Pharm*. 1986;5:471-480. 7. Ziegler VE, Clayton PJ, Biggs JT. A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry*. May 1977;34:607-612.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities

required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdose, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C. and lower clearance of nortriptyline.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported. A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension,

tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone marrow depression, including agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling, elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

[PAM-Z17-1/13/89]



Dorsey Division

SANDOZ PHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500



Emergency medicine.

Management of severely disruptive behavior: Ativan® Injection with a neuroleptic.

Rapid tranquilization with a wider margin of safety.

Although neuroleptic agents provide an effective means of controlling violent or destructive behavior, their use is associated with a risk of serious and potentially irreversible adverse effects.¹⁻² Dose reduction is the best way to minimize this risk, but such a solution may not be possible during an emergency. The use of ATIVAN Injection combined with a low-dose neuroleptic provides an alternative pharmacologic approach for sedating anxious and agitated patients exhibiting severely disruptive behavior.

Clinical experience with this combination suggests that effective

control can be achieved with lower neuroleptic doses than when using a neuroleptic alone.³

Ativan® Injection: Pharmacologically desirable as an adjunct for sedation.

Unlike other benzodiazepines, ATIVAN Injection is readily absorbed following intramuscular administration,⁴ with peak plasma concentrations occurring in approximately 60 to 90 minutes.⁵ Mean half-life is about 16 hours and the desired sedative and anxiolytic effects usually last 6 to 8 hours.^{5*}

*The additive central-nervous system effects of neuroleptics should be borne in mind when used concomitantly with ATIVAN Injection.

Please see the adjacent page for a brief summary of prescribing information.

Ativan® Injection I.M.

(lorazepam) 

**Calm the patient,
curtail adverse reactions.**

ATIVAN® INJECTION I.M. (LORAZEPAM) Ⓒ

DESCRIPTION: Ativan® (lorazepam) injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(6-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative. **CLINICAL PHARMACOLOGY:** IV or IM administration of recommended dose of 2 to 4 mg lorazepam injection to adult patients is followed by dose-related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling preoperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15 to 20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6 to 8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse (See **WARNINGS** and **ADVERSE REACTIONS**).

Clinically employed doses of lorazepam injection do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8 to 10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with penicillin 150 and 75 mg. Although this study showed both lorazepam and penicillin 150 and 75 mg with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—For preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation (See **WARNINGS**).

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION, THEREFORE, EQUIPMENT TO MAINTAIN PATIENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and sexual excretion of conjugated lorazepam (glucuronide) is renal, lorazepam is not recommended in hepatic and/or renal failure. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care to patients given injectable lorazepam since premature mobilization may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlorazepoxide, diazepam, meperbromate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastrocnemius, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concomitant control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss to rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g., phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection (See **CLINICAL PHARMACOLOGY** and **WARNINGS**). Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See **WARNINGS** and **DOSAGE AND ADMINISTRATION**). When lorazepam is used IV as premedication prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose (See **ADVERSE REACTIONS**).

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g., sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedication that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials, no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g., narcotic analgesics, inhalation anesthetics, scopolamine, atropine and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility. **Pregnancy:** Pregnancy Category D. See **WARNINGS** section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with cardiac anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see **DOSAGE AND ADMINISTRATION**). On rare occasions (3/1580), patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropiate behavior (after seen most commonly when scopolamine given concomitantly as premedication). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately postinjection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/445) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary under-ventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also **CLINICAL PHARMACOLOGY, WARNINGS** and **PRECAUTIONS**).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over a prolonged period of time may result in limited physical and psychological dependence.

OVERDOSEAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases ataxia, hypotonia, hypotension, hypoxia, stages one to three coma and, very rarely, death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injections: For designated indications as premedication, usual IM doses of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedications, individualize dose (See also **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS** and **ADVERSE REACTIONS**). Doses of other CNS depressants should ordinarily be reduced. (See **PRECAUTIONS**). For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure. Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injections: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given (See **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS** and **ADVERSE REACTIONS**). Doses of other CNS depressants should ordinarily be reduced (See **PRECAUTIONS**). For optimum effect, measured as lack of recall, IV lorazepam should be administered 15 to 20 minutes before anticipated operative procedure. EQUIPMENT NECESSARY TO MAINTAIN A PATIENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (See **WARNINGS**). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP; Sodium Chloride Injection, USP; 5% Dextrose Injection, USP.

BOW SUPPLIER: Ativan® (lorazepam) injection, Wyeth, is available in single- and multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 1 ml and 10 ml vials and 1 ml fill in 2 ml TUBEX.

4 mg/ml, NDC 0008-0570; 1 ml and 10 ml vials and 1 ml fill in 2 ml TUBEX.

For IM or IV injection. Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogeneous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

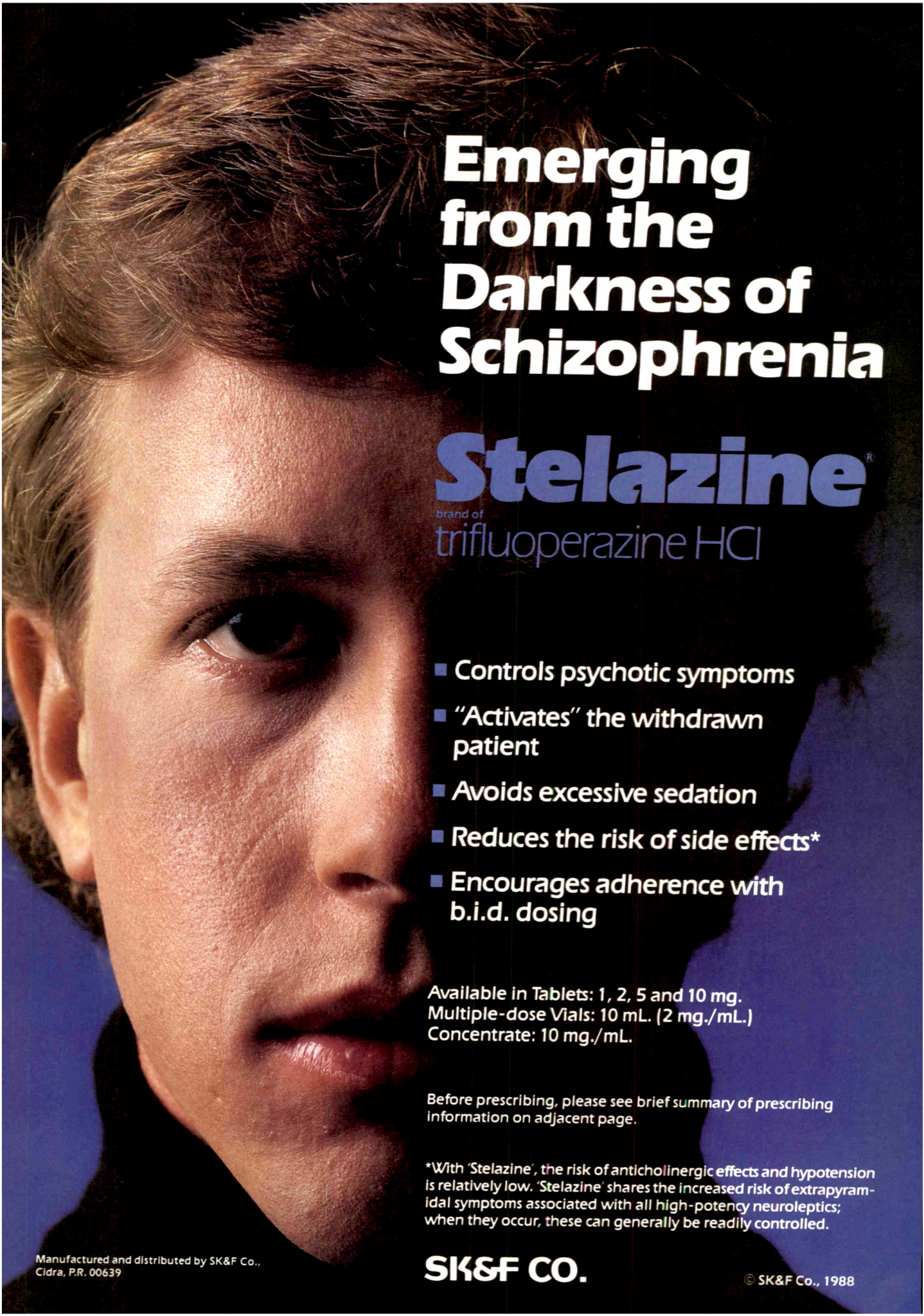
CI 3261-2 6/22/83

References:

- Graham R, Günther W, Ruther E: Adverse effects of psychotropic drugs. In Hippis H, Winokur G (eds): *Clinical Psychopharmacology*. Amsterdam: Excerpta Medica, 1963, pp 378-385.
- Dubin WR: Rapid tranquilization: Antipsychotics or benzodiazepines? *J Clin Psychiatry* 1988;49(suppl):5-11.
- Selzman C, Green AI, Rodriguez-Villa F, et al: Benzodiazepines combined with neuroleptics for management of severe disruptive behavior. *Psychosomatics* 1986;27(suppl):17-21.
- Harvey SC: Hypnotics and sedatives. In Gilman AG, Goodman LS, Rall TW, et al (eds): *The Pharmacological Basis of Therapeutics*, ed 7. New York: Macmillan Publishing Company, 1985, pp 339-371.
- Data on file, Wyeth-Ayerst Laboratories.

**WYETH-AYERST
LABORATORIES**
Philadelphia, PA 19101

© 1989, Wyeth-Ayerst Laboratories



Emerging from the Darkness of Schizophrenia

Stelazine[®]
brand of
trifluoperazine HCl

- Controls psychotic symptoms
- "Activates" the withdrawn patient
- Avoids excessive sedation
- Reduces the risk of side effects*
- Encourages adherence with b.i.d. dosing

Available in Tablets: 1, 2, 5 and 10 mg.
Multiple-dose Vials: 10 mL (2 mg./mL.)
Concentrate: 10 mg./mL.

Before prescribing, please see brief summary of prescribing information on adjacent page.

*With 'Stelazine', the risk of anticholinergic effects and hypotension is relatively low. 'Stelazine' shares the increased risk of extrapyramidal symptoms associated with all high-potency neuroleptics; when they occur, these can generally be readily controlled.

Stelazine®

brand of
trifluoperazine HCl

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecostasia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

SK&F CO.

Manufactured and distributed by
SK&F Co., Cidra, P.R. 00639

BRS-SZ-L63

© SK&F Co., 1988

PSYCHIATRIST

OPPORTUNITY WITH CENTRAL FLORIDA PSYCHIATRIC HOSPITAL

PARK PLACE HOSPITAL, a 60-bed private psychiatric facility in Central Florida, is offering a position for a board certified or board eligible psychiatrist. Located just outside **Orlando, Florida**—one of the nation's fastest growing metropolitan areas — Park Place Hospital is close to all major tourist attractions; beaches; and recreational, civic and cultural activities and events. Central Florida offers diversity in lifestyle, a warm climate year round and unlimited opportunity for career growth and success.

PARK PLACE HOSPITAL OFFERS:

- * Opportunity for private practice and salaried medical administration position.
- * New office building located near hospital facility.
- * Outstanding compensation package, including paid relocation.

Please call or send curriculum vitae

 **Park Place Hospital**
206 Park Place Boulevard, Kissimmee, Florida 32741
407-846-0444
Equal Opportunity Employer

PSYCHIATRIST

Swope Parkway Health Center has an immediate opening for a full-time/part-time psychiatrist. Must be board-certified or board-eligible. Must be licensed in Missouri.

Swope Parkway Health Center is JCAHO-accredited, ambulatory health center and a community mental health center providing a wide range of mental health services including:

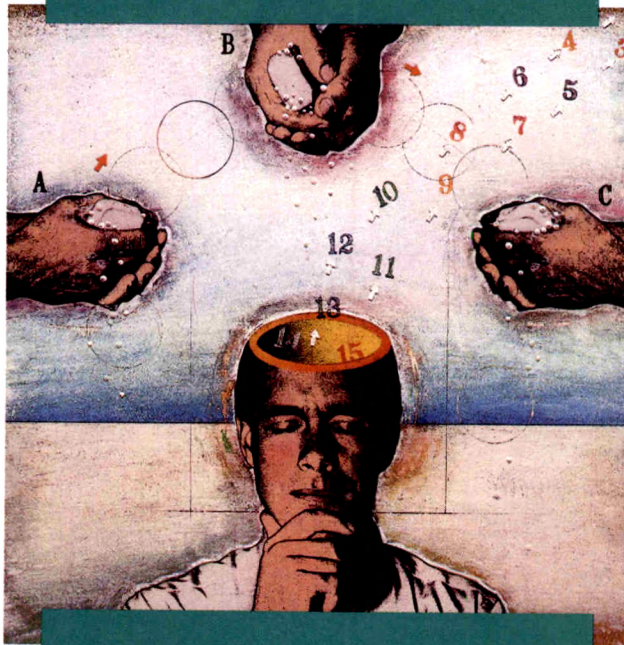
- outpatient
- drug and alcohol
- partial hospital
- children's services
- residential care
- various preventive programs

In addition, the Health Center provides services in pediatrics, internal medicine, OB/GYN, podiatry, dental, and optometry services. Hospital privileges in two area hospitals. Center provides malpractice, CME, health/life insurance, pension, disability, holidays, and competitive salary.

Send curriculum vitae to:

Cheryl Kelow
Personnel Director
Swope Parkway Health Center
4900 Swope Parkway
Kansas City, MO 64130
(816) 923-4545, ext. 225

CIBA-GEIGY ANNOUNCES



FDA procedures now bring promising investigational drugs to patients earlier in the development process.

The Food and Drug Administration has established procedures to allow use of "...promising drugs for treatment of patients with serious or life-threatening illnesses..."¹ as early in the drug development process as possible and before general marketing has begun.

This OCD medication is the first psychotropic drug authorized under these new procedures.

In releasing the drug for treatment use, the FDA explained that "...studies aimed at U.S. approval... have shown sufficient evidence of effectiveness for the drug to permit its limited distribution."²

A treatment IND (investigational new drug) program for patients with Obsessive- Compulsive Disorder

For information and enrollment kits call
1-800-842-2422
between 9AM-5PM Eastern Time

Ready supply of drug available through enrolled psychiatrists for eligible patients.

The treatment medication is being distributed by CIBA-GEIGY free of charge to psychiatrists enrolled in the treatment IND program, who will, in turn, supply the drug to eligible patients.

Patient enrollment criteria established.

Patients must be between 10 and 70 years of age, with OCD symptoms of at least one year's duration that interfere significantly with daily functioning.

¹ Young FE, Benson JS, Nightingale SL, et al: Drugs available under treatment IND. *FDA Drug Bulletin* 1988;18:14-15.

² FDA Press Release, June 6, 1988.

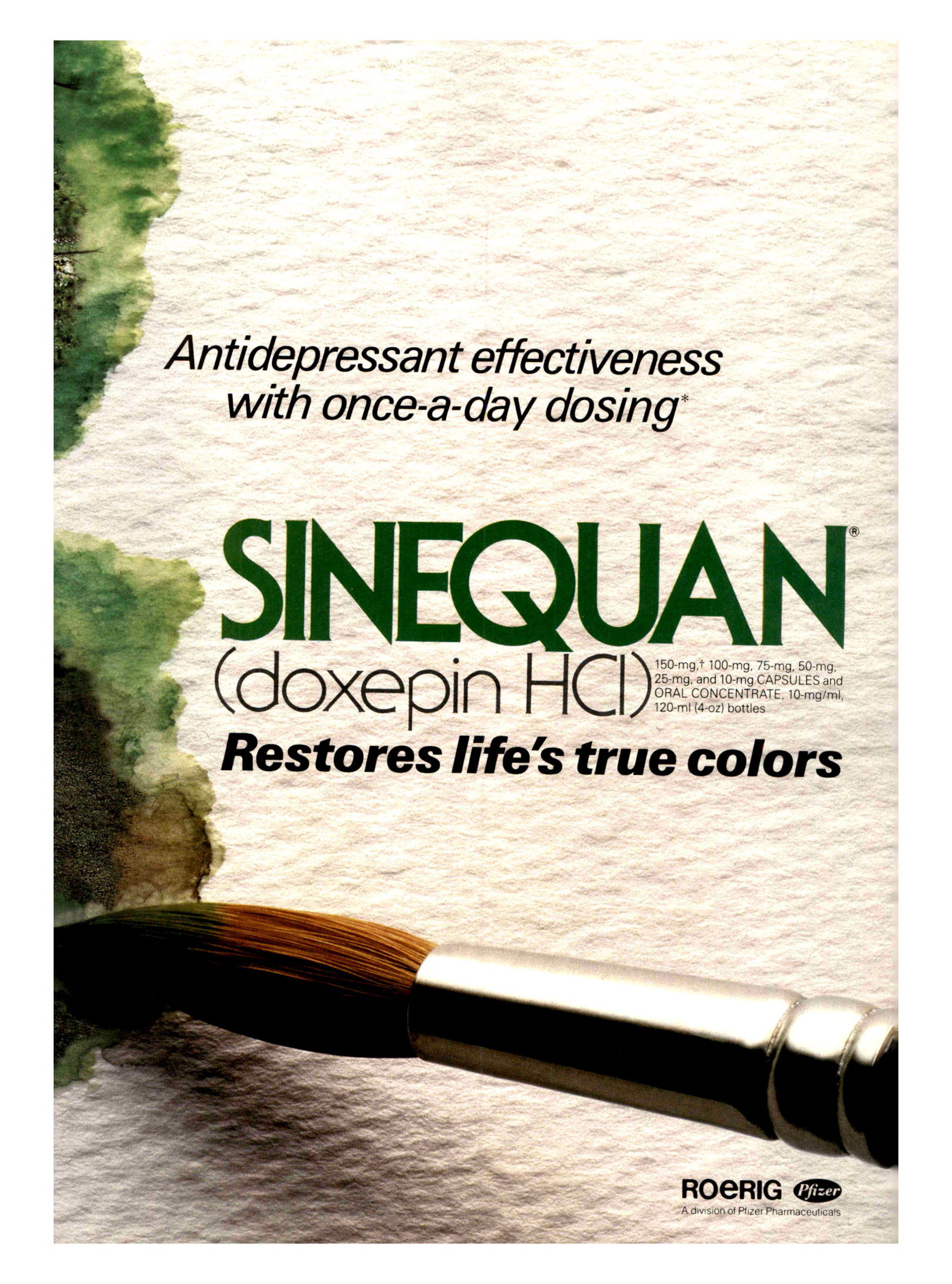


*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

© 1985, Pfizer Inc.



*Antidepressant effectiveness
with once-a-day dosing**

SINEQUAN[®]

(doxepin HCl)

150-mg,† 100-mg, 75-mg, 50-mg,
25-mg, and 10-mg CAPSULES and
ORAL CONCENTRATE, 10-mg/ml,
120-ml (4-oz) bottles

Restores life's true colors

ROERIG 

A division of Pfizer Pharmaceuticals

SINEQUAN® (doxepin HCl)

BRIEF SUMMARY

SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

ROERIG 

A division of Pfizer Pharmaceuticals
New York, New York 10017

PSYCHIATRISTS

BOSTON

Fulltime and parttime psychiatrists sought for exciting mix of public and private practice. Academic appointment at the Boston University Medical Center for qualified applicants, opportunity for research and private practice and inpatient/ambulatory care at public mental health facility. Opportunity to be part of a growing group practice with ownership of stock available. A non-profit low overhead research institute is affiliated with the practice to accept grants for physicians. Superb compensation package includes fringe benefits tailored to individual needs. Minority and Spanish-speaking physicians especially sought.

Send CV in confidence to:
Richard Pillard, M.D.
Boston Psychiatric Group, P.C.
Room 905 JP
85 E. Newton St.
Boston, MA 02118.

An Affirmative Action Employer.

**HEAD,
DEPARTMENT OF PSYCHIATRY**
University of Illinois College of Medicine at Chicago

**CHIEF,
DEPARTMENT OF PSYCHIATRY**
Michael Reese Hospital and Medicine Center

The University of Illinois College of Medicine at Chicago and Michael Reese Hospital and Medical Center invite applications and nominations for the position of Head/Chief of the Department of Psychiatry. The Head/Chief will lead the Psychiatry program of two of Chicago's most important medical institutions, both with a long history of academic excellence and outstanding patient care. The Department of Psychiatry is also affiliated with programs at the West Side Veterans Administration, the Illinois State Psychiatric Institute and the Institute for Juvenile Research.

Candidates should be Diplomates of the American Board of Psychiatry and Neurology (or equivalent), have had substantial scholarly productivity in the field, and have demonstrated ability to provide dynamic leadership in administering a comprehensive program of patient care, education, and research in Psychiatry.

Interested individuals should send a curriculum vitae to:

Edward L. Applebaum, M.D.
Chairman, Search Committee
Professor and Head, Department of Otolaryngology
—Head and Neck Surgery
University of Illinois College of Medicine at Chicago
1855 West Taylor Street
Chicago, IL 60612

The University of Illinois at Chicago is an affirmative action/equal opportunity employer

Calendar

(Continued from page A16)

October 9–11, 2nd congress, World Association for Psychosocial Rehabilitation, Barcelona, Spain. Contact J.L. Marti-Tusquets, University of Barcelona, Casanova 143, Barcelona 08036, Spain.

October 10–14, 8th International Forum of Psychoanalysis, Rio de Janeiro, Brazil. Contact ADAM Congressos e Eventos Ltda., 63, Av. Almirante Barroso, Grps. 1413-1414, Rio de Janeiro 20031, R.J., Brazil; 021-220-2781.

October 11–15, annual meeting, American Academy of Child and Adolescent Psychiatry, New York. Contact Virginia Q. Anthony, Executive Director, 3615 Wisconsin Avenue, NW, Washington, DC 20016; 202-966-7300.

October 12–14, annual meeting, American Academy of Medical Administrators, Scottsdale, Arizona. Contact Thomas R. O'Donovan, Ph.D., President, 30555 Southfield Road, Suite 150, Southfield, MI 48076; 313-540-4310.

October 13–15, 6th International Conference on Multiple Personality/Dissociative States, Chicago. Contact Bennett G. Braun, M.D., Program Director, ICMP/DS, Rush-Presbyterian-St. Luke's Medical Center, 6130 North Sheridan Road, Chicago, Illinois 60660; 312-508-6440 or 508-6442.

October 13–19, 8th World Congress of Psychiatry, World Psychiatric Association, Athens, Greece. Contact Dr. Constantinos R. Soldatos, Department of Psychiatry, Eginition Hospital, 74 Vassilissis Sophias Avenue, Athens 11528 Greece; 30 1 72 23 670.

October 14–16, annual meeting, Association of Mental Health Librarians, Philadelphia. Contact Emily Bergman, President, 2235 Beverly Boulevard, Los Angeles, CA 90057; 213-483-7034.

October 15–18, 4th International Congress on Headache, Sydney, Australia. Contact Conference Action Pty. Ltd., 88 Albany Street, Crows Nest, Sydney 2065, Australia.

October 15–20, annual meeting, American College of Surgeons, Atlanta. Contact Paul A. Ebert, M.D., Director, 55 East Erie Street, Chicago, IL 60610; 312-664-4050.

October 16–17, annual meeting, Institute of Medicine/National Academy of Sciences, Washington, DC. Contact Samuel O. Thier, M.D., President, 2101 Constitution Avenue, NW, Washington, DC 20418; 202-334-2169.

October 18–21, annual meeting, American Academy of Clinical Psychiatrists, St. Louis. Contact Alicia A. Muñoz, Exec-

utive Secretary, P.O. Box 3212, San Diego, CA 92103; 619-298-4782.

October 18–22, 28th World Congress on Epilepsy, New Delhi. Contact Dr. K.S. Mani, 1 Old Vety, Hospital Road, Bangalore, 560004 India.

October 19–22, annual meeting, American Academy of Psychiatry and the Law, Washington, D.C. Contact Jonas R. Rappeport, M.D., Medical Director, 1211 Cathedral Street, Baltimore, MD 21201; 301-539-0379.

October 21–26, annual meeting, American Academy of Pediatrics, Chicago. Contact James E. Strain, M.D., Executive Director, P.O. Box 927, Elk Grove Village, IL 60009-0927; 312-288-5005.

October 22–27, 24th World Congress on Neurology, New Delhi. Contact Dr. J.S. Chopra, Organizing Secretary, 1033 Sector 24 B, Chandigarh 160 023, India.

October 22–27, annual meeting, American Health Care Association, New Orleans. Contact Paul R. Willging, Ph.D., Executive Vice-President, 1200 15th Street, N.W., 8th Floor, Washington, DC 20005-2899; 202-833-2050.

October 25–29, annual meeting, American Academy for Cerebral Palsy and Developmental Medicine, San Francisco. Contact John A. Hinckley, Executive Director, P.O. Box 11086, Richmond, VA 23230; 804-355-0147.

October 26–28, annual meeting, Milton H. Erickson Foundation, Inc., Phoenix. Contact Jeffrey K. Zeig, Ph.D., 3606 North 24th Street, Phoenix, AZ 85016; 602-956-6196.

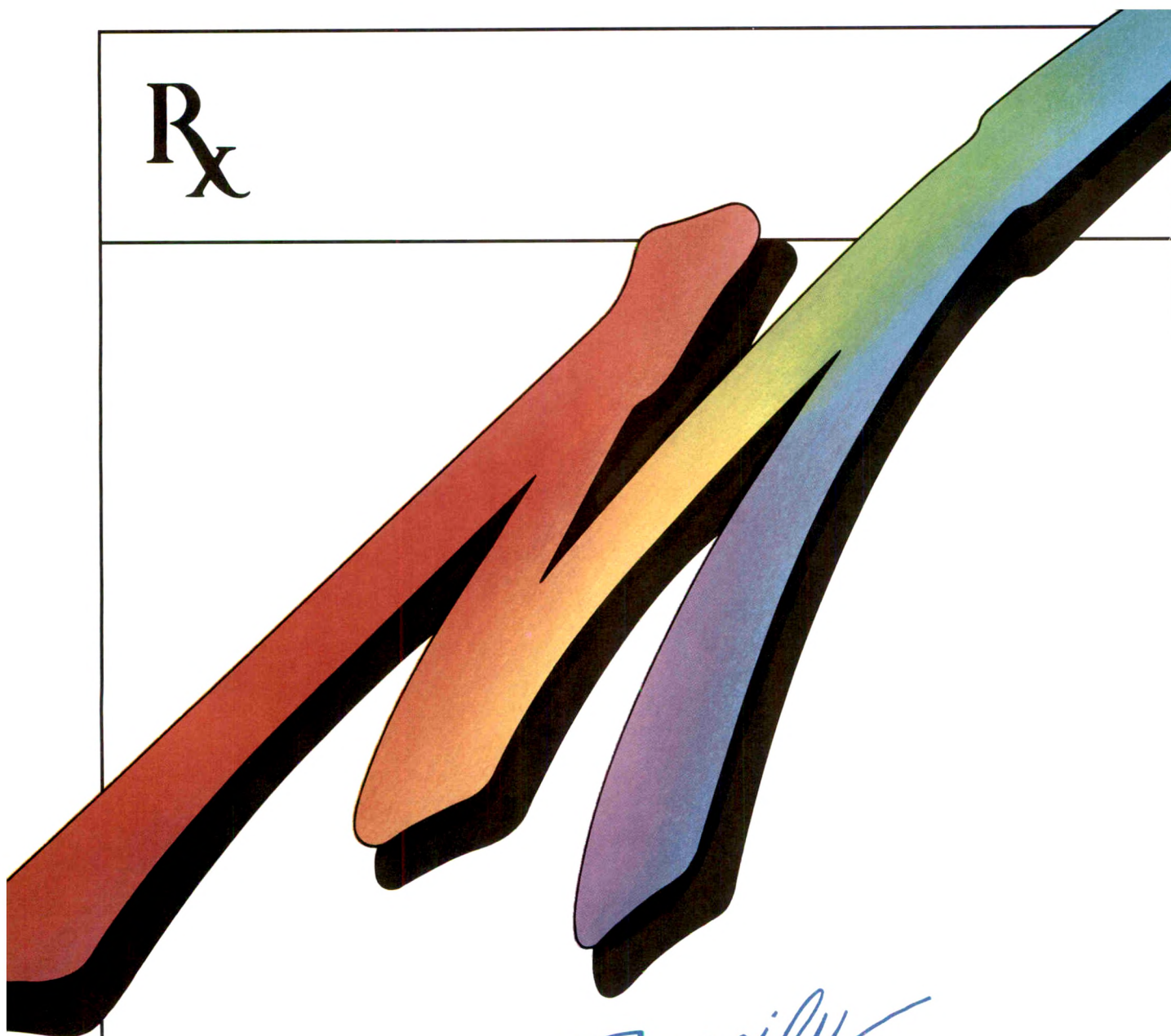
October 26–29, 47th annual conference, American Association for Marriage and Family Therapy, San Francisco. Contact AAMFT, Department C, 1717 K Street, NW, #407, Washington, DC 20006; 202-429-1825.

October 26–29, annual meeting, Academy of Psychosomatic Medicine, Las Vegas. Contact Evelyne Hallberg, Executive Director, 5824 N. Magnolia, Chicago, IL 60660; 312-784-2025.

October 28–November 2, annual meeting, Association of American Medical Colleges, Washington, DC. Contact Robert G. Petersdorf, M.D., President, One Dupont Circle, N.W., Suite 200, Washington, DC 20036; 202-828-0400.

October 29–November 3, annual meeting, Society for Neuroscience, Phoenix, Arizona. Contact Nancy Beang, Executive Director, 11 Dupont Circle, N.W., Suite 500, Washington, DC 20036; 202-462-6688.

R_x



Protect Your Prescription

Specify

Dispense as Written

Mellaril[®]
(thioridazine)



Dorsey Division
SANDOZ PHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

© 1987 Sandoz Pharmaceuticals Corporation

MEL-887-1



10 mg



15 mg



25 mg



50 mg



100 mg



150 mg



200 mg



30 mg/ml



100 mg/ml



25 mg/5 ml



100 mg/5 ml

More Laws for Better Medicine?

Although common sense has always dictated to physicians as well as to ordinary citizens the obligation to protect potential victims by removing them from a dangerous situation or by warning them about the existence of a danger, it was the *Tarasoff* decision in 1974 (1) that made psychiatrists acutely aware of the potential liability for violent acts committed by their patients. The possibility that one might bear serious psychological, professional, and financial consequences in response to what a court of justice might consider an error of clinical judgment would provoke anxiety in any reasonable human being.

The article by Appelbaum and associates, elsewhere in this issue, on the possible approaches to restricting psychiatrists' liability for breach of duty to predict provides us with an extensive review of the existing statutes, as well as a clear presentation and an analysis of the APA's resource document on the physician's duty to take precautions against patient violence.

The proposed model statute is intended to relieve some of the anxiety that was generated in clinicians by the *Tarasoff* and similar decisions. Indeed, the proposed modifications to the legal doctrine on the duty to warn may reduce the level of anxiety by clarifying the issue and limiting the conditions under which psychiatrists can be held liable. However, more legislation may be a high price to pay to alleviate that anxiety.

The first question Appelbaum and associates try to answer is, when does the duty to protect potential victims arise? After stating that the physician has an inescapable ethical obligation to protect an endangered person, the authors suggest legislation by which liability for failure to protect such a person would be prohibited except under specified circumstances. Those circumstances amount to an actual threat, identifiable victims, intent, and ability to carry out the threat. Only when those elements were present and the psychiatrist decided not to do whatever was necessary to protect the victim would liability be considered. This may well give us all a false sense of reassurance. What if one, two, three, or all of those essential elements were missing and a horrible tragedy happened because the physician, having based his or her judgment and decision on those elements, did not proceed with the necessary steps? There is, indeed, a danger that some clinicians may view those four elements as the only indicators to be used in assessment of dangerousness. There is also the possibility that courts of justice will use them as a test against which our decisions will be evaluated.

The second question is, how can the duty to protect be discharged? What appears to be a simple, logical corollary to the ethical obligation to protect becomes, again, an occasion to propose that specific measures be enshrined in statutes. Psychiatrists who have reason to be concerned about the safety of a designated victim would have the choice of taking one of the following steps: warn the victim, notify law enforcement authorities, attempt to commit the patient, hospitalize the patient voluntarily, or take any other reasonable step, including "such reasonable precautions to prevent the threatened harm as would be taken by a reasonably prudent [physician] under the same circumstances." One may question whether legal guidelines are needed to supplement what has been accepted for centuries as sound medical ethics.

To Appelbaum and associates' third question—what protections are provided for physicians who attempt to discharge their duty under the statutes?—the APA's

model statute states that physicians who by doing so have disclosed confidential information should be given immunity. At first sight, this amounts to legalizing the breach of confidentiality. Once again, it is an intrusion of law into one of the most sacred territories of medicine, and it may, at least in theory, affect the doctor-patient relationship, the decision-making process, and quality of care.

Appelbaum and associates' position and the APA model statute illustrate well the trend we may have inadvertently started by requesting and even assisting legislators to step in further in an issue that may initially have been left to the clinical judgment of the therapist. The "codification" of certain aspects of our decision-making process, as self-protective as it may appear, opens the door to more unsolicited over-seeing and control.

In addition, as Appelbaum and associates have aptly pointed out, there is a risk that some clinicians will use the recommended legal criteria, instead of broadly defined medical criteria, in the formulation of an opinion regarding dangerousness and in the formulation of a treatment plan. At a time when the debate still rages about what constitutes mental illness and the criteria to distinguish a potentially dangerous individual from a probably dangerous individual remain to be determined, it may be tempting to ask the legal system to provide us with a new frame of reference. At a time when we are challenged from the inside and the outside, when we are sued for treating too much and not enough, and when science fails to answer many of our questions; especially when it comes to help us in "predicting" the future behavior of an individual who may harm other people, it may indeed be tempting to opt out and let a written text sanctioned by the law take care of our doubts.

It is interesting to observe from a forensic psychiatric perspective how the burden of responsibility for wrongdoing has gradually shifted from the doer, to the devil, to insanity, and now to psychiatrists. However, it may be premature for lawmakers and professional psychiatric associations to assume that clinical psychiatrists have already endorsed the principle of shared responsibility concerning predetermined conditions. The time may have come to reconsider whether the marriage between law and psychiatry has not created a prejudice to one of the parties.

REFERENCE

1. Tarasoff v Regents of the University of California, 529 P 2d 553 (Cal 1974)

PIERRE GAGNÉ, M.D.

Dr. Gagné is Director, Forensic Unit, Sherbrooke Hospital. Address reprint requests to Dr. Gagné, Sherbrooke Hospital, Sherbrooke, Que. J1J 3H5, Canada.

Statutory Approaches to Limiting Psychiatrists' Liability for Their Patients' Violent Acts

Paul S. Appelbaum, M.D., Howard Zonana, M.D., Richard Bonnie, J.D.,
and Loren H. Roth, M.D., M.P.H.

A consensus has developed among mental health professionals that the legal duty to protect potential victims of their patients' violent acts, as fashioned by the courts, requires modification. To date, 12 states have responded with legislation designed to clarify and limit clinicians' responsibilities. In addition, APA has distributed a model statute as a resource document to aid those psychiatrists interested in stimulating legislative action. This paper examines existing statutes and the APA resource document, considers the variety of ways in which the goals of reform can be achieved, and recommends approaches that balance desires for public safety with the legitimate needs and concerns of the mental health professions.

(Am J Psychiatry 1989; 146:821-828)

Nearly a decade and a half have passed since the initial decision of the California Supreme Court in *Tarasoff v. Regents of the University of California* (1). That opinion, later modified when the case was reheard (2), first recognized a duty on the part of mental health professionals to protect potential victims of their outpatients' violent acts. One version or another of a *Tarasoff*-like duty has since been adopted by courts in roughly a score of American jurisdictions (3).

From the first, the duty to protect enunciated in *Tarasoff* has been subject to criticism from mental

health professionals (4). Although survey evidence suggests that most clinicians are willing to accept some degree of ethical obligation to protect potential victims (5, 6), the vagueness and breadth of the *Tarasoff*-like legal duties have drawn considerable fire. In particular, attention has focused on standards governing when the legal duty to protect comes into play and by what mechanisms it can be discharged (7).

The California Supreme Court decreed that the duty was triggered when a therapist "determines, or pursuant to the standards of his profession should determine, that his patient presents a serious danger of violence to another" and that the duty is discharged by the therapist taking whatever steps are "reasonably necessary" to protect the intended victim. Critics have focused on the lack of professional standards for determining when a patient is likely to be violent, as well as on the indeterminate scope of a duty for which all steps that are reasonably necessary must be taken. The latter is seen as vague and susceptible to retrospective bias.

Precisely what the impact has been of *Tarasoff* and the cases that have followed its reasoning is subject to dispute. It has been argued that a duty to protect discourages patients from coming to therapy, or once there from speaking freely, for fear that their confidentiality will be breached, as it was in *Tarasoff* itself (4). In addition, it is claimed that interventions undertaken to protect potential victims often have little protective effect (8) and that fear of liability may drive therapists away from treating potentially violent patients (9). Sufficient empirical evidence to test these assertions is lacking.

On the other hand, it appears clear that no court decision in the last generation has succeeded in so raising the anxieties of mental health professionals. The ill-defined nature of the duty to protect has led to great confusion about clinicians' obligations (10). Some

Received July 26, 1988; accepted Dec. 23, 1988. From the Departments of Psychiatry, University of Massachusetts Medical School, Worcester, Yale University School of Medicine, New Haven, Conn., and University of Pittsburgh School of Medicine, Pittsburgh; and the University of Virginia Law School, Charlottesville. Address reprint requests to Dr. Appelbaum, Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA 01655.

Copyright © 1989 American Psychiatric Association.

therapists appear to be overreacting in their efforts to protect potential victims, with others attempting to avoid any contact with potentially violent patients. This state of anxiety has been stimulated further by several court decisions that have imposed liability in situations in which most therapists would conclude that there was little that could have been done to predict or prevent the violence that ensued (11).

A consensus thus has developed among mental health professionals that some modification of the duty to protect is warranted. Although some court decisions have taken clinical concerns into account in structuring a restricted duty to protect (e.g., references 12–14), the mental health professions increasingly have sought legislative relief. Specifically, they have requested statutory limitations on liability for failure to protect patients' victims. California was the first to adopt such a statute in 1985, and 11 other states, at last count, have followed suit (15–26).

Recognizing the need for careful consideration of prospective legislation, APA's Council on Psychiatry and Law reviewed possible approaches to statutory limitation of the duty to protect. Its efforts, with which we were involved, led to the production of a model statute on which legislation to restrict the duty might be based (appendix 1). The statute, which was distributed by APA as a resource document, does not imply endorsement by the organization of even a limited legal duty to protect. Rather, it is based on a recognition that many jurisdictions are considering statutes that address the duty and that an appropriate model might be of use in those states to mental health professionals and legislators alike. The goal of the drafters was to accommodate the widely recognized imperative for clinicians to take protective actions, while clarifying the scope of the duty and the means of discharging it, in a manner that takes into account realistic limitations on clinicians' capacities to predict and prevent violent acts.

In this paper we discuss the possible approaches that might be taken to restrict liability for breach of the duty to protect, comparing them with existing statutes and with the APA resource document. Our goal is to offer clinicians who might be considering the introduction of such legislation in their states an overview of the advantages and disadvantages of possible courses of action. We focus on the three major questions that any statute must address: When does the duty to protect arise, how can the duty be discharged, and what protections are provided for clinicians who attempt to discharge their duties under the statute?

WHEN DOES THE DUTY ARISE?

Although some mental health professionals would undoubtedly prefer to be relieved of any risk of liability arising from the violent acts of their patients, few legislatures are likely to follow the lead of Ohio, which stands alone in abrogating the common-law duty to

protect (24)—a duty that has been recognized in some form by virtually every court that has confronted the issue. Further, as noted earlier, there is good reason to believe that most mental health professionals would agree that they have some ethical obligation to protect endangered persons. They might be willing to accept a corresponding legal duty if the boundaries of that obligation could be clearly and reasonably defined. Thus, almost all legislation on the subject has aimed to clarify and restrict the duty to protect rather than to abrogate it entirely.

Establishing a Duty

Some statutes explicitly establish a duty to protect (table 1) and, in doing so, preclude further judicial expansion of the duty beyond the circumstances specified in the statute. However, other statutes, as well as the APA resource document, take a conceptually different approach: They prohibit liability except under the specified circumstances, without stating that a duty does arise when those circumstances are present. At first glance, the difference between a statute that creates a duty and one that limits a duty without establishing one might seem obscure. The latter approach, however, leaves open the possibility that courts that have not yet recognized a common-law duty to protect might decline to do so at all. At the least, this approach provides preemptive protection against judicial imposition of a broad and ill-defined duty to protect. Even in states, such as California, where the courts have already imposed a duty to protect, "permissive" language would allow leeway for judicial abrogation of the duty in the future (however unlikely that course might seem at present), without requiring legislative action. Overall, then, statutes that do not explicitly establish the existence of a duty to protect are preferable from clinicians' point of view.

Requiring an Actual Threat

The most common mechanism for clarifying the circumstances under which a duty to protect arises is to limit it to situations in which patients have made actual threats of violence. Almost every state that has enacted legislation has adopted this approach, although the wording differs from jurisdiction to jurisdiction. The APA resource document requires "an explicit threat to kill or seriously injure"; California requires a "serious threat of physical violence"; Montana and Utah use the language of "actual threat"; Colorado specifies "a serious threat of imminent physical violence," and Louisiana an "immediate threat," thereby injecting a time dimension into the requirement of a threat. Indiana has taken a different tack, adding as an alternative to an actual threat the additional circumstance of a patient's evidencing conduct or making statements indicating an imminent danger to others; although this still requires some threatening behavior on the patient's part, it is a considerably

TABLE 1. Provisions of APA and State Statutes Regulating the Duty to Protect

Provision	APA	Calif.	Colo.	Ind.	Ky.	La.	Mass.	Minn.	Mont.	N.H.	Ohio ^a	Utah	Wash.
Origination of duty													
Establishes duty				Yes	Yes	Yes	Yes ^b	Yes ^c	Yes	Yes		Yes	Yes
Actual threat	Yes	Yes	Yes		Yes	Yes	Yes ^d	Yes	Yes	Yes		Yes	Yes
Identifiable victims only	Yes	Yes	Yes			Yes	Yes	Yes	Yes	Yes		Yes	Yes
Property threatened	Yes ^e									Yes			
Intent and ability to act	Yes					Yes							
Discharge of duty													
Warn victim or police	Yes			Yes			Yes	Yes	Yes	Yes		Yes	
Warn victim and police		Yes	Yes ^f		Yes	Yes							Yes
Attempt to commit patient	Yes			Yes	Yes		Yes			Yes ^g		Yes	
Hospitalize patient voluntarily	Yes		Yes										
Other reasonable steps	Yes		Yes	Yes ^h									
Protections for clinicians													
Immunity for disclosure	Yes		Yes	Yes	Yes	Yes		Yes	Yes	Yes		Yes	
Other													
Negligent release excluded	Yes		Yes					Yes ⁱ					

^aOhio statute precludes liability for failure to protect in all circumstances.

^bStatute defines duty only for licensed psychologists.

^cStatute defines duty only for nonphysician mental health professionals.

^dActual threat not required if patient has history of physical violence.

^eDuty applies only when destruction of property is likely to lead to serious personal injury or death.

^fProvisions do not apply in face of negligent failure to initiate involuntary commitment of imminently dangerous mentally ill person.

^gCommitment must actually be obtained to discharge duty.

^hDuty discharged if reasonably available steps taken to prevent violence while police are summoned.

ⁱStatute does not apply to involuntarily committed patients.

broader standard than the others. Massachusetts requires an actual threat except when the patient has a known history of physical violence.

The actual threat limitation is the most direct attempt to answer the objections of mental health professionals to *Tarasoff's* requirement that they act to protect when they "should have known" the patient was dangerous. The recurrent question has been, "When should we have known that the patient was likely to be violent (given the absence of the definitive professional standards assumed to exist by the *Tarasoff* court)?" The new statutes respond, "Only when an actual threat has been made." At least one court has created similar limitations on the duty to protect (13). The homology to the requirement for an "overt act" in many commitment statutes should be noted; there, too, this approach was taken, at least in part, to provide an objective evidentiary foundation for predictions of future dangerous behavior (27).

Although this modification of the duty is protective of mental health professionals, it may arouse concern among those who recognize that violence might be foreseeable even in the absence of an explicit threat. A therapist who has knowledge of, or experience with, a patient's previous violent behavior might identify a confluence of factors that have led to violence in the past (e.g., delusions of persecution and an increase in alcohol consumption). Statutory efforts to define when a duty arises are therefore caught on the horns of a dilemma. On one hand, the "should have known" standard employed by the *Tarasoff* court is uncertain in scope and therefore potentially *overinclusive* because clinicians might make disclosures to protect themselves from liability even if they do not believe the patient is

likely to be dangerous. On the other hand, the category of "explicit threats" is admittedly *underinclusive* because it does not cover some circumstances in which protective action on the part of a therapist might well be called for.

This dilemma highlights the tension in drafting duty-to-protect statutes between a desire to be maximally protective of potential victims and concerns about unreasonable imposition of liability and severe disruption of the clinical process. Given the uncertainties inherent in prediction of future violence (28), and the vagueness inherent in any open-textured phrase that might be used in its stead, we believe the "explicit threat" approach is preferable. In choosing this option, however, we recognize that the goal of protecting the public may be compromised to some degree for the sake of valid competing interests. It should also be emphasized that these statutes do not preclude therapists from acting to protect potential victims in circumstances other than those involving actual threats; indeed, the APA resource document and the Minnesota statute explicitly recognize that such circumstances might occur and expressly *permit* protective action to be taken when they do. But in the absence of an actual threat, protective action is not mandatory and no liability will ensue for failure to act.

Restricting the Duty to Identifiable Victims

Tarasoff itself dealt with a situation in which the victim was readily identifiable by the patient's therapists. The court limited the duty it imposed there to those persons who were clearly identified or identifiable on a moment's reflection (2). Most courts have

followed suit, although some have extended the duty to include nonidentifiable victims as long as the harm itself could be said to have been reasonably foreseeable (29, 30). The statutes enacted to date and the APA resource document are nearly unanimous in requiring that victims be identifiable. Some statutes, such as Louisiana's, limit the duty to "a clearly identified victim or victims," while others, such as New Hampshire's, broaden it to include "a clearly identified or reasonably identifiable victim or victims." The latter term is similar to *Tarasoff's* phrase that the person be identifiable on "a moment's reflection." Only Kentucky and Indiana take different approaches. Kentucky invokes the duty to protect both when victims are identifiable and when "the patient has communicated . . . an actual threat of some specific violent act," even if the victims are not specified. Whether Kentucky's provision is in fact different from the others, however, is unclear.

The test case might involve a patient who threatens to spray Main Street with bullets and whose therapist does not attempt to prevent him or her from carrying out the plan. If the narrower statutes are construed according to their plain meaning, the therapist would be immune from liability—a paradoxical result, since specification by the patient of even one person who might be on the street at the time would have invoked the duty to protect. One wonders, however, whether a court faced with this situation would not construe the class of people likely to be on Main Street as a group of identified or reasonably identifiable victims. Although this would broaden the concept of identifiability to the point where it all but merges with foreseeability, there would be a certain logic to this. Kentucky's language represents a more sensible approach to this problem, since it excludes general threats to the public safety (e.g., as manifested by dangerous driving behavior, which might exceed the practical limits of predictability) but includes situations in which the threatened act has been specified.

Indiana's statute is unique in failing to require either identifiable victims or a specific violent act: It requires action if the patient "evidences conduct or makes statements indicating an imminent danger that the patient will use physical violence or use other means to cause serious personal injury or death to others." This language is disturbingly vague and likely to perpetuate confusion about when the duty to protect exists.

Including Threats to Property

The duty to protect—insofar as it focuses on the behavior of outpatients—has traditionally been interpreted as referring to the prevention of violence to the person, a limitation that almost all the current statutes make explicit. One court, however, has applied the *Tarasoff* rationale to property destruction involving arson of a barn by an outpatient (31). The implicit rationale for the usual limitation to acts of personal violence would appear to be that mere destruction of

property does not warrant breach of therapeutic confidentiality, with all the presumed harms involved. APA's resource document invokes the duty when patients threaten "to destroy property under circumstances likely to lead to serious personal injury or death," an extension consistent with the overall purpose of the duty to protect. New Hampshire, however, goes a step further, extending the duty to "a serious threat of substantial damage to real property." How much damage is "substantial" is unclear, inviting suit against therapists to test the extent of this exception.

Requiring Intent and Ability to Act

Properly construed, the duty to protect never required therapists to take action merely because a threat was made. Threats that therapists deemed unlikely to be acted upon did not invoke the duty to protect because no harm was foreseeable. There has been some confusion about this among therapists, however, with an unfortunate tendency in some cases to act first and think through the situation afterward (10). Some statutes that actually create a duty to protect appear, by their wording, to exacerbate this problem. Thus, Montana's law states that a mental health professional has a duty to protect when an "actual threat of physical violence by specific means" is made. Unless "actual" is taken to mean a threat that is likely to be acted upon—a reading that requires some contortion of the plain meaning of the word—the statute would appear to imply that even threats that clinicians conclude are not likely to be acted on require some protective action.

To avoid the problem of an overinclusive obligation, some states and the APA's resource document specify that the patient must have "the apparent intent and ability to carry out the threat." As with other provisions of duty to protect statutes, this grant of discretion to clinicians is a double-edged sword. It protects patients and therapists from needless breach of confidence or other unwarranted protective action, but only by requiring the exercise of judgment in difficult circumstances that might later be challenged. Should a clinician argue that he or she failed to take steps to protect a potential victim, even in the face of an explicit threat, because the clinician doubted the intent or ability of the patient to follow through on the threat, the clinician's judgment would be subjected in court to retrospective review by experts for each side of the case. Still, the requirement that some judgment be exercised seems unavoidable if automatic disclosure of patients' threats is not to be endorsed.

HOW CAN THE DUTY BE DISCHARGED?

Narrowing and clarifying the situations in which the duty to protect arises would respond to only a portion of the criticism lodged against the doctrine. A good deal of concern has been generated by the breadth of the resulting duty, often characterized as requiring th

taking of all reasonable steps to protect potential victims. This formulation of the duty leaves the clinician perpetually uncertain whether the duty has been adequately discharged. In addition, it opens the door to imposition of "strict" liability for having failed to prevent violence; in retrospect it will be difficult to resist the conclusion that whatever steps were taken by the clinician were inadequate because they failed to avert the harm and that some additional "reasonable" measures ought to have been implemented.

Thus, it should not be surprising that every statute to date (except Ohio's, which, as noted earlier, precludes liability for failure to protect in all circumstances) has addressed these problems by specifying the measures by which the duty can be discharged. Except where noted later in this article, these measures fulfill the duty disjunctively; that is, any single measure is sufficient by itself to discharge the clinician's obligation.

Warning the Victim

This is one of the most frequent measures employed by therapists to protect endangered victims; indeed, many clinicians misconstrue the duty to protect as being equivalent to a duty to warn (6), perhaps because this was the holding of the original *Tarasoff* decision (1). That opinion was superseded by a revised opinion that established a broader duty to protect (2). Every statute (except Ohio's unique law) permits the duty to be discharged at least partially in this way, although nearly half the laws mandate that an additional measure—warning an appropriate law enforcement agency—be undertaken in conjunction with it. (There is some irony in mental health professionals' current support for statutes that create a duty to warn as expressed in the first *Tarasoff* decision, given the adverse reactions it aroused when first promulgated.)

The statutes, with the exception of Minnesota's, limit the clinician's obligation to making "reasonable efforts" to contact the potential victim, recognizing that in some circumstances victims cannot be located. This seems preferable when statutes establish a conjunctive duty to notify law enforcement authorities but unduly lax when such efforts discharge the duty entirely. In the latter case, a clinician may be said to have discharged the duty without succeeding in notifying the potential victim or taking other protective measures. The APA resource document, which contains several disjunctive means of discharging the duty, is better construed here, requiring *actual* notification of the potential victim. Failing that, some other means of fulfilling the duty to protect must be sought.

Warning Law Enforcement Authorities

All statutes under which a duty to protect may be recognized allow at least partial discharge of the duty by warning appropriate police agencies, although as noted earlier, this is frequently coupled with a requirement that efforts be made to see that the potential

victim is also notified. Some legislatures have provided little guidance as to which law enforcement agencies should be notified, using only the term "appropriate," as in Colorado, or omitting any modifier whatsoever, as in California. Other statutes specify the agency in the vicinity of the patient's or victim's residence. Kentucky requires notification of the local police in both the patient's and the victim's locales, since these will often differ. Kentucky's statute, it will be recalled, also extends the duty to nonidentifiable victims when a specific act is threatened. In that case, the duty is discharged by contacting "law enforcement authorities." Oddly, several of the statutes require only "reasonable efforts" to contact law enforcement agencies—an anomaly, since it is difficult to see how even minimal efforts could fail. This again exemplifies the tension one sees in these statutes between rules that are maximally protective of clinicians and those which give priority to protection of potential victims.

Attempting to Commit the Patient

Five states (Indiana, Kentucky, Massachusetts, New Hampshire, and Utah) and the APA resource document permit efforts at involuntary hospitalization to discharge the duty. Indiana, Massachusetts, and Utah ask that the clinician "seek" commitment; Kentucky requires only "reasonable efforts" in this direction; and the APA document speaks of "legally appropriate steps to initiate proceedings for involuntary hospitalization." In contrast, New Hampshire requires the clinician to "obtain civil commitment of the client to the state mental health system." The requirement that a clinician only initiate commitment recognizes that patients will frequently be transferred to other facilities for a decision on emergency commitment (sometimes called "certification" and usually in the power of designated clinicians to effect). Not only will the original clinician not have the determining voice, but he or she may lose track of the patient once referral has taken place. On the other hand, a "reasonable efforts" standard again leaves open the possibility that no action even minimally protective of the victim might be taken, yet the clinician will be deemed to have discharged the duty. Requiring clinicians to convey information concerning the patient's threat to the clinician with responsibility for deciding on emergency commitment—with that person then assuming responsibility for necessary protective action—could close the logical gap here.

No statutes require commitment of dangerous patients; all allow the duty to be discharged in other ways. A recent Federal Court of Appeals decision in a *Tarasoff*-like case similarly refused to find that psychiatrists had a "duty to commit" (14). Colorado's statute, however, may effectively create such a duty by excluding from immunity the negligent failure to initiate emergency involuntary commitment for patients who meet commitment criteria on the basis of danger to others. This would appear to undercut the other

provisions of the statute by allowing clinicians' judgments to be challenged retrospectively unless they have elected to seek commitment.

Hospitalizing the Patient Voluntarily

Colorado and the APA resource document recognize voluntary hospitalization (Colorado's statute just speaks of hospitalization) as a means of discharging the duty to protect. Presumably, as in the case of civil commitment, the original clinician's obligation does not recur when the patient is discharged, but transmission of a new threat (or perhaps other evidence of dangerousness—see the following discussion of the applicability of these statutes to inpatient settings) invokes a duty on the part of the inpatient therapist. To the extent that a brief hospitalization “launders” the patient's threat, relieving both outpatient and inpatient clinicians of further responsibility despite the possibility of continuing risk, this approach would not appear maximally protective of potential victims. But imposing a continuing obligation on an outpatient clinician (e.g., an emergency room psychiatrist who heard the threat and initiated hospitalization) who is unlikely to have further contact with the patient makes little sense either. The obligation should be transferred to the inpatient clinician when that person is informed of the original threat.

Taking Other Reasonable Steps

As noted, all extant statutes except Ohio's specify ways in which the duty to protect can be discharged. The language of some statutes suggests that the list of options presented is an exclusive one (e.g., the California statute states that “the duty shall be discharged by the psychotherapist making reasonable efforts to communicate the threat to the victim or victims and to a law enforcement agency”). This suggests that other protective action, such as hospitalizing the patient, may still leave the clinician open to liability if violence occurs. To the extent that a statute specifies an exclusive list of measures that discharge the duty, clinicians can be certain whether or not they have taken legally sufficient measures. On the other hand, such specification may encourage use of only a limited repertoire of responses when other measures may be clinically indicated in the service of patients' needs. For example, a statute that only endorses warning the potential victim and/or the police encourages clinicians to breach confidentiality as a first resort, although they might prefer to take more clinically oriented measures, such as using psychotherapy to focus on the threat, starting medication, or even hospitalizing the patient (32).

Even under statutes with language suggesting an exclusive list of options, it may be possible for a therapist to argue that some other action was taken to deal reasonably with the situation and thus that an allegation of negligence is unfounded. That possibility, however, may not be apparent to most clinicians. Some statutes

have more open-ended wording, more clearly suggesting that the enumerated options may not be the only legitimate possibilities. In addition, one statute and the APA resource document both indicate expressly that other appropriate actions may discharge the duty to protect. Colorado's law accepts “other appropriate action including, but not limited to, hospitalizing the patient” as one route for discharging the duty to protect. The APA model requires physicians to “take such reasonable precautions to prevent the threatened harm as would be taken by a reasonably prudent [physician] under the same circumstances” and notes that such “precautions include, but are not limited to, those specified” in the statute. This may be the best way of drafting the statute, providing certainty for those therapists who desire to discharge their duty cleanly but making clear that clinicians who choose to act otherwise may do so, as long as their actions are justifiable under ordinary, professional standards. This is a departure from the case law in some jurisdictions, in which protective actions taken by a therapist are judged according to lay standards of reasonableness (2, 30).

WHAT PROTECTIONS ARE PROVIDED FOR CLINICIANS WHO ATTEMPT TO DISCHARGE THEIR DUTY UNDER THE STATUTE?

Since the statutes concerning the duty to protect create or endorse duties that may conflict with other obligations of therapists, including protection of patient confidentiality, most statutes make some attempt to resolve this apparent contradiction.

The majority of current statutes provide explicit immunity for disclosures designed to fulfill the duty to protect. Louisiana's language is illustrative: “No liability or cause of action shall arise against any psychologist or psychiatrist based on an invasion of privacy or breach of confidentiality for any confidence disclosed to a third party in an effort to discharge the duty arising under [this statute].” A difficulty with most such provisions is that they limit immunity to discharge of duties arising under the statute, meaning when an overt threat is made toward (almost always) an identifiable victim. The language appears to indicate that if a therapist desires to breach confidentiality when he or she believes someone to be endangered, but no actual threat has been made, such disclosures would not be afforded immunity. This exclusion fails to advance the interest in protecting potential victims or in limiting unreasonable liability. The APA resource document deals with this problem by granting immunity for disclosure not only when the patient has made explicit threats but also when the clinician “otherwise concludes that a patient is likely to” cause “serious harm to person or property.” (Some states may have permissive language that has the same effect in statutes that do not otherwise define a duty to protect [e.g., reference 33].)

APPLICABILITY TO INPATIENT SETTINGS

Colorado's law and the APA resource document make explicit a significant limitation on the duty-to-protect statutes, excluding from coverage patients who are discharged from inpatient care. Minnesota similarly excludes patients who have been involuntarily committed. Although the rationale for these exclusions is unstated, liability for the behavior of inpatients substantially predates the imposition of an outpatient duty to protect in *Tarasoff*. The two lines of cases have become interwoven in recent years, but there is still a tendency to hold inpatient clinicians to higher standards when violence results from allegedly negligent release. Justification may derive from several factors, including the belief that hospitalization affords clinicians greater opportunity to observe and become aware of the violent proclivities of their patients. The fact that inpatient clinicians have established actual control over their patients, along with an implied promise of effective treatment, may also contribute to the higher standard applied to inpatient settings.

There are reasons intrinsic to the logic of the duty-to-protect statutes that might warrant disparate treatment of inpatient settings. Should clinicians be immune from liability, for example, if, having in custody a threatening patient with the intent and ability to carry out the threatened act, they discharge him or her but are courteous enough to warn the potential victim? It seems clear to us that the answer should be "No." At the least, one might want to expand the situations in which a duty exists and alter the obligations of the inpatient therapist. Unfortunately, with the exception of Colorado and Minnesota, none of the jurisdictions shows any evidence of having considered whether different standards might apply to inpatient settings, and even the two exceptional statutes fail to specify what those standards might be. This is an issue to which subsequent drafting efforts might profitably pay heed.

CONCLUSIONS

Legitimate concerns about the judicial characterization of a legal duty to protect potential victims of a patient's violent acts have led psychiatrists and other mental health professionals to urge legislative redefinition of the duty. These efforts have already led to success in nearly 25% of the states. Yet, the enacted statutes vary greatly in the scope and effect of their provisions, with some being much more compatible with the flexibility required to provide excellent clinical care. The APA resource document embodies many of the most useful provisions of such statutes. Rather than supporting any measure that purports to restrict liability from the duty to protect, mental health professionals ought to examine proposed legislation carefully, advocating the inclusion of those provisions which best balance the complex interests involved.

REFERENCES

1. *Tarasoff v Regents of the University of California*, 529 P 2d 553 (Cal, 1974)
2. *Tarasoff v Regents of the University of California*, 551 P 2d 334 (Cal, 1976)
3. Beck JC: The psychotherapist's duty to protect third parties from harm. *Mental & Physical Disability Law Reporter* 1987; 11:141-148
4. Brief for Amici Curiae, American Psychiatric Association et al, *Tarasoff v Regents of the University of California*, 551 P 2d 334 (Cal, 1976)
5. Wise TP: Where the public peril begins: a survey of psychotherapists to determine the effects of *Tarasoff*. *Stanford Law Rev* 1978; 135:165-190
6. Givelber D, Bowers W, Blitch D: *Tarasoff*, myth and reality: an empirical study of private law in action. *Wisconsin Law Rev* 1984;443-497
7. Appelbaum PS: Rethinking the duty to protect, in *The Potentially Violent Patient and the Tarasoff Decision in Psychiatric Practice*. Edited by Beck JC. Washington, DC, American Psychiatric Press, 1985
8. Halleck SL: *Law in the Practice of Psychiatry*. New York, Plenum, 1980
9. Gurevitz H: *Tarasoff*: protective privilege versus public peril. *Am J Psychiatry* 1977; 134:289-292
10. Appelbaum PS: *Tarasoff* and the clinician: problems in fulfilling the duty to protect. *Am J Psychiatry* 1985; 142:425-429
11. Appelbaum PS: The expansion of liability for patients' violent acts. *Hosp Community Psychiatry* 1984; 35:13-14
12. *Hasenei v US*, 541 F Supp 999 (1982)
13. *Brady v Hopper*, 570 F Supp 1313 (D Colo, 1983)
14. *Currie v US*, number 86-2643 (4th Cir, Dec 28, 1987)
15. California Civil Code, Section 43.92
16. Colorado Revised Statutes, Section 13-21-117
17. Indiana Statutes Annotated Code, Section 34-4-12.4
18. Kentucky Revised Statutes, Section 202A.400
19. Louisiana Revised Statutes Annotated, Section 9:2800.2
20. Massachusetts General Laws Annotated, Chapter 112, Section 129
21. Minnesota Statutes, Section 148.975-148.976
22. Montana Code Annotated, Section 27-1
23. New Hampshire Revised Statutes Annotated, Section 329.31
24. Ohio Revised Code Annotated, Section 5122.34
25. Utah Code Annotated, Section 78-14a-102
26. 1987 Washington Legislative Service, 212
27. *Lessard v Schmidt*, 349 F Supp 1078 (ED Wis, 1972)
28. Monahan J: *The Clinical Prediction of Violent Behavior*. Rockville, Md, National Institute of Mental Health, 1981
29. *Lipari v Sears, Roebuck and Co*, 497 F Supp 185 (D Neb, 1980)
30. *Petersen v Washington*, 671 P 2d 230 (Wash, 1983)
31. *Peck v Counseling Service of Addison County, Inc*, 499 A 2d 422 (Vt, 1985)
32. Roth LH, Meisel A: Dangerousness, confidentiality, and the duty to warn. *Am J Psychiatry* 1977; 134:508-511
33. Florida Statutes, 455.2415

APPENDIX 1. American Psychiatric Association's Model Statute on the Physician's Duty to Take Precautions Against Patient Violence

Developed by the Council on Psychiatry and Law and approved by the Board of Trustees in June 1987, this resource document does not represent official APA policy but rather is offered as a guide to District Branches in those states in which case law has expanded the potential "duty to protect" liability of psychiatrists.

Section __. Duty of [Physicians] to Take Precautions Against Patient Violence.

1. *Scope of cause of action*. Except as provided in para-

graph 5, no cause of action shall lie against a [physician], nor shall legal liability be imposed, for breaching a duty to prevent harm to person or property caused by a patient unless a) the patient has communicated to the [physician] an explicit threat to kill or seriously injure a clearly identified or reasonably identifiable victim or victims, or to destroy property under circumstances likely to lead to serious personal injury or death, and the patient has the apparent intent and ability to carry out the threat; and b) the [physician] fails to take such reasonable precautions to prevent the threatened harm as would be taken by a reasonably prudent [physician] under the same circumstances. Reasonable precautions include, but are not limited to, those specified in paragraph 2.

2. *Legally sufficient precautions.* Any duty owed by a [physician] to take reasonable precautions to prevent harm threatened by a patient is discharged, as a matter of law, if the [physician] either a) communicates the threat to any identified victim or victims; or b) notifies a law enforcement agency in the vicinity where the patient or any potential victim resides; or c) arranges for the patient to be hospital-

ized voluntarily; or d) takes legally appropriate steps to initiate proceedings for involuntary hospitalization.

3. *Immunity for disclosure.* Whenever a patient has explicitly threatened to cause serious harm to person or property, or a [physician] otherwise concludes that a patient is likely to do so, and the [physician], for the purpose of reducing the risk of harm, discloses any confidential communications made by or relating to the patient, no cause of action shall lie against the [physician] for making such disclosure.

4. *Definitions.*

a. For purposes of this [section], "patient" means any person with whom a [physician] has established a [physician]-patient relationship.

b. For purposes of this [section], ["physician"] means a person licensed to practice medicine in this state.

5. *Limited applicability of this section.* This section does not modify any duty to take precautions to prevent harm by a patient that may arise if the patient is within the custodial responsibility of a hospital or other facility or is being discharged therefrom.

Seasonality and Affective Illness

Thomas A. Wehr, M.D., and Norman E. Rosenthal, M.D.

The authors review what has been learned about the causes, symptoms, and treatments of seasonal affective disorder and discuss its relevance to affective illness in general. They point out that seasonal and environmental influences on depression have been themes in writings on affective illness for more than 2,000 years and that there has been a resurgence of interest during the past decade. There appear to be two primary, opposite seasonal patterns of annual depression—winter depression and summer depression—with opposite vegetative symptoms. Seasonal affective disorder is not uncommon. It is important to identify patients with winter depression because they respond to a specific treatment, phototherapy.

(Am J Psychiatry 1989; 146:829–839)

Whoever wishes to pursue the science of medicine in a direct manner must first investigate the seasons of the year and what occurs in them.

—Hippocrates (1, p. 2)

During the past decade there has been increasing interest in a seasonal form of affective illness characterized by recurrent winter depressions. This interest was stimulated by evidence that winter depression is accompanied by a distinctive constellation of symptoms, including overeating, oversleeping, and carbohydrate craving; that it is triggered by light deficiency; and that it responds to a novel type of treatment, phototherapy (2). A recent analysis of scientific citations (3) identified studies of seasonal affective disorder as one of the most rapidly growing areas of biomedical research. In recognition of these developments, *DSM-III-R* now includes seasonal subtypes of affective disorders.

The end of the first decade of intensive research on seasonal affective disorder seems an appropriate time to review what has been learned about the causes, symptoms, and treatments of seasonal forms of affective illness and to examine the relevance of these findings to affective illness in general.

In spite of the apparent novelty of seasonal affective disorder, there is an extensive historical record on the subject. The historical record, which we have reviewed, is surprisingly consistent with modern observations about seasonality.

REGULAR SEASONAL PATTERNS OF RECURRENCE OF AFFECTIVE ILLNESS

The observation that affective illness is sensitive to seasonal and environmental influences was central to ancient theories about the etiology of disease (4). Hippocrates (5) taught that “it is chiefly the changes of the seasons which produce diseases, and in the seasons the great changes from cold or heat” (p. 123). According to Roccatalgiata (6), Posidonius, writing in the fourth century A.D., summarized the views of many ancient physicians with regard to affective illness when he noted that “melancholy occurs in autumn whereas mania in summer” (p. 143). The ancient physicians believed that this pattern was produced by seasonal changes in temperature acting on body humors. As Aristotle (7) explained, “Black bile . . . when it is overheated . . . produces cheerfulness accompanied by song and frenzy . . . if it be cold beyond due measure, it produces groundless despondency; hence suicide by hanging occurs” (p. 954).

It has long been recognized that some individuals regularly experience depressive episodes on an annual basis. These individuals appear to conform to one of two, opposite seasonal patterns—recurrent winter depression or recurrent summer depression. In other seasons these same individuals may be less severely depressed, euthymic, hypomanic, or manic. The idea that different individuals might react in opposite ways to the seasons was discussed in a general way by Hippocrates (5), who observed that “of constitutions some are well or ill adapted to summer, others are well or ill adapted to winter” (p. 123). However, in the early nineteenth century, Pinel and his student Esquirol may have been the first to delineate winter and summer subtypes of depression. Pinel (8) wrote that “maniacal paroxysms . . . generally begin immediately after the summer solstice, . . . are continued . . . during the heat of summer, and commonly terminate towards the decline of autumn . . . The high excitement . . . is now exchanged for . . . a most profound melancholy” (p. 10). He noted that an opposite pattern could occur “in

Received March 8, 1988; revision received Dec. 7, 1988; accepted Dec. 20, 1988. From the Clinical Psychobiology Branch, National Institute of Mental Health. Address reprint requests to Dr. Wehr, Clinical Psychobiology Branch, NIMH, Rm. 4S-239, Bldg. 10, 9000 Rockville Pike, Bethesda, MD 20892.

which the paroxysms returned upon the approach of winter" (p. 10). Similarly, Esquirol (9) observed that "there are individuals who pass the summer in a state of prostration or agitation; whilst in the winter they are in an opposite condition" (p. 32), and he described a number of patients with each pattern.

To our knowledge, the earliest examples of individuals with the two, opposite seasonal patterns of affective recurrence are from the seventeenth century. According to Dewhurst (10), Ann Grenville, an English noblewoman, appears to have suffered for many years from regularly recurring winter depressions and summer manias. Her physician wrote that "there are twin symptoms, which are her constant companions, mania and melancholy, and they succeed each other in a double and alternate act." "Mania," he observed, "breaks all bonds . . . each year during the dog days." According to Philips (11), the English poet John Milton may have had a type of regularly recurring summer depression. Milton confided to an acquaintance "that his vein never happily flowed but from the autumnal equinoctial to the vernal, and that whatever he attempted [in summer] was never to his satisfaction . . . so that all the years he was about this poem [*Paradise Lost*], he may be said to have spent but half his time therein."

After Pinel and Esquirol, many other leading psychiatrists of the nineteenth and twentieth centuries (12–19) published histories of patients with recurrent winter depressions and patients with recurrent summer depressions. Griesinger (12) noted the existence of "cases where regularly at one particular season—for example, in winter—a profound melancholia has supervened, which in spring passes into mania, which again in autumn gradually gives way to melancholia" (p. 163). Kraepelin (15) wrote that he "repeatedly . . . saw in these cases moodiness set in in autumn and pass over in spring" (p. 139). Kraepelin (16) stated that "in the typical cyclic case, there are two attacks in each year, one manic and one depressive . . . the onset of one phase tends to occur in the spring, and the opposite phase in the fall" (p. 78). Seasonal patterns of recurrence can also be detected in records of the longitudinal course of recurrent affective illness published by various investigators who did not comment on seasonality (20).

During the past decade there has been a resurgence of interest in seasonal influences on affective illness. In 1982, Lewy et al. (21) described an individual with recurrent winter depression. In 1984, Rosenthal et al. (2) reported on their systematic investigation of a series of patients with winter depression and delineated the clinical features of the syndrome. They developed operational criteria for the diagnosis of seasonal affective disorder and presented evidence for its validity based on a distinctive course, clinical and demographic features, and response to a specific treatment, phototherapy. This evidence has been replicated in its essentials by several other groups (22–25). Wehr et al. (26) systematically investigated a series of patients with summer depression and, in agreement with Boyce and

Parker (25), described symptoms that in some respect appear to be opposite to those of winter depression. Results of other recent research (27, 28) are consistent with these findings. Wehr et al. (20) also describe patients who had a combination of the two seasonal patterns with two depressions per year, one in the winter and one in the summer.

Thase (29), Montplaisir (30), and Garvey et al. (24) found prevalences of individuals attending clinics specializing in the treatment of recurrent depression who met criteria for seasonal affective disorder of 16%, 29% and 38%, respectively. If valid, these results suggest that many patients with seasonal affective disorder go unrecognized in these settings. Correct diagnosis could be important because of the treatment implications: patients with winter depression respond to phototherapy.

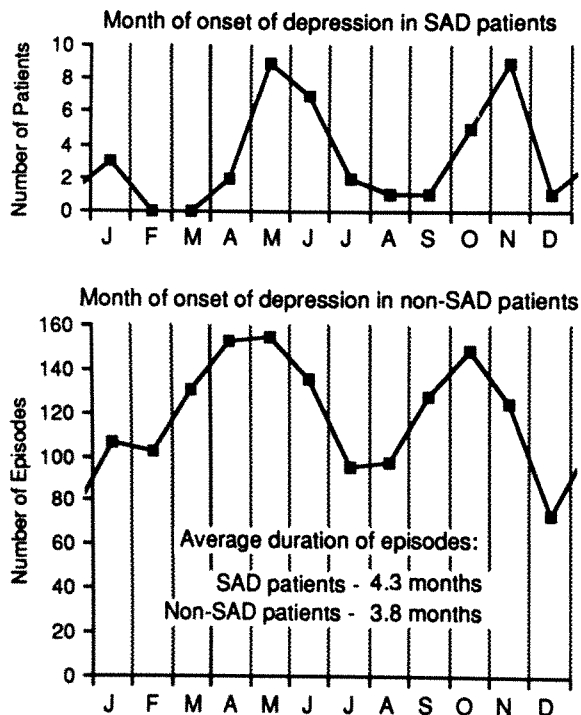
There is as yet little evidence concerning the prevalence of seasonal affective disorder in the general population. Recently, Kasper et al. (27) used structured telephone interviews to survey a representative sample of the general population of Montgomery County, Md., a suburb of Washington, D.C. Their results suggest that about 5% of this sample experienced seasonal symptoms of depression that were as severe as those experienced by patients enrolled in a seasonal depression clinic.

There appears to be a spectrum of severity of seasonal episodes. At one extreme an individual's depressions or manias may be so severe as to require hospitalization (20). On the other hand, many individuals who neither meet criteria for major affective disorder nor seek treatment for their symptoms appear to experience mild seasonal mood swings that interfere with their productivity and well-being (15, 17, 25–28). These individuals with subsyndromal winter depressions merit attention because they seem to benefit from phototherapy (31).

The evidence that has been cited so far to support the concept of two, opposite seasonal subtypes of depression emerged from studies of clinical groups in which selection biases and observer biases may not have been controlled. To confirm the validity of these subtypes, epidemiologic studies are required. In this regard, in their Montgomery County survey, Kasper et al. (27) confirmed previous clinical impressions by finding that individuals who experience regular seasonal recurrences of depressive symptoms exhibit either winter or summer patterns. Other investigators (28; unpublished 1989 paper of Rosen et al.) obtained similar results when questionnaires were mailed or administered to representative samples of the general population of four East Coast U.S. cities. Similar results were also obtained in an Australian survey (25).

Thus, the classical psychiatric literature, recent investigations of clinical groups, and surveys of the general population all suggest that some depressions can regularly recur on an annual basis and that these annual depressions usually exhibit one of two opposite seasonal patterns, a summer type and a winter type. Although these findings have been rather consistent

FIGURE 1. Month of Onset of Depression in Patients With (N=40) or Without (N=274) Seasonal Affective Disorder (SAD)^a



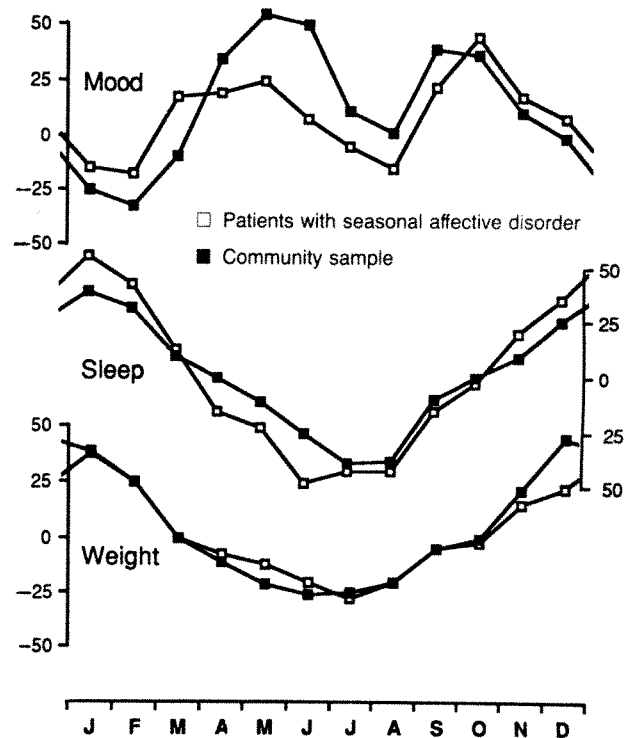
^aThe group with seasonal affective disorder consisted of 20 patients with summer depression and 20 patients with winter depression (26). The diagram shows the number of patients whose depressions typically began during each month. The group without seasonal affective disorder consisted of patients with endogenous or involuntal depression reported by Angst et al. (32). The diagram shows the number of episodes that began during each month.

date, they need to be confirmed in more rigorous and more extensive epidemiologic studies.

CONTRASTS BETWEEN SUMMER DEPRESSION AND WINTER DEPRESSION

In the Washington, D.C., area, winter depressions usually begin in November and end in March, and summer depressions usually begin in May and end in September (2, 20, 26) (figure 1). In addition to their opposite times of occurrence, the two types of depression appear to have opposite types of symptoms. In 1984, Rosenthal et al. (2) noted that patients with winter depression often experienced "atypical" depressive symptoms, such as oversleeping, overeating, carbohydrate craving, and weight gain. Subsequently, Wirz-Justice et al. (22), Thompson and Isaacs (23), and Garvey et al. (24) reported similar findings. In 1988, in a survey based on questionnaires sent by mail, Boyce and Parker (25) also confirmed the finding of atypical symptoms in individuals who regularly experienced depressive symptoms in the winter, and they reported a trend for typical or endogenous symptoms, such as insomnia and loss of appetite and weight, in individu-

FIGURE 2. Seasonal Changes in Mood, Sleep Duration, and Weight in Patients With Seasonal Affective Disorder (N=40) and in a Random Sample of the Population of New York City (N=212)^a



^aThe group with seasonal affective disorder consisted of 20 patients with summer depression and 20 patients with winter depression (26) (the same patients shown in figure 1). The group without seasonal affective disorder was a randomly selected sample of the population of New York City studied by Terman (28). The graph shows for each month the relative proportion of individuals in each group experiencing changes in mood (percent elevated minus percent depressed), sleep duration (percent increased minus percent decreased), and weight (percent increased minus percent decreased). The bimodal winter and summer troughs in the mood graph are due to an increase in the number of individuals who were depressed at these times of the year. The unimodal patterns of the weight and sleep graphs are due to the fact that relatively more individuals gain weight and sleep more in the winter.

als who regularly experienced depressive symptoms in the summer. Wehr et al. (26) found similar differences between winter and summer depressions in a study in which they used structured diagnostic interviews and clinical rating scales to evaluate clinical features of depression prospectively in 20 individuals with winter depression and 20 individuals with summer depression. In addition, many of their patients with summer depression, unlike those with winter depression, had coexisting lifetime diagnoses of anxiety disorders.

Although the vegetative changes in summer and winter depressions are often opposite, their evolution through the cycle of the year is parallel. Both groups of patients sleep more and gain weight in winter and sleep less and lose weight in summer. In fact, similar changes through the year have been described in a random sample of the general population (28) (figure 2).

The contrasting clinical pictures of summer and win-

ter depressions are reminiscent of the contrasting pictures in dichotomous classifications of depression, such as endogenous versus reactive, psychotic versus neurotic, and typical versus atypical (V type) (33). These subtypes represent contrasting syndromes with increased sleep versus decreased sleep and weight gain versus weight loss. Many studies (26) found that increased sleep was associated with weight gain and decreased sleep with weight loss, as was found in winter depression and summer depression.

Winter depression appears to be precipitated by light deficiency and responds to treatment with light (2, 21–23, 28, 31, 34–51). The cause of summer depression is not firmly established, but anecdotal reports and results of preliminary experiments (20, 26) point to heat as one possible triggering factor. Our clinical observations suggest that winter depressions are longer and more severe at high latitudes (2) but that summer depressions are longer and more severe at low latitudes (20). Furthermore, results of a recent three-center study (unpublished 1989 paper of Rosen et al.) suggest that the ratio of patients with winter depression to patients with summer depression increases with increasing latitude.

SENSITIVITY TO THE PHYSICAL ENVIRONMENT: IMPLICATIONS FOR TREATMENT

Observations that season and latitude can influence the course of affective illness have two important implications. First, changes in the physical environment may precipitate affective episodes. Second, modifications of the physical environment might be used to treat affective episodes. In previous eras, many physicians recognized these implications and devised environmental treatments for their patients. One approach was “climatotherapy,” which involved traveling to a different latitude and climate. For example, Esquirol (9) successfully treated a patient’s winter depression by suggesting that he “be in Italy before the close of October, from whence you must not return until the month of May” (p. 226).

Since the time of Hippocrates (52), physicians have suggested manipulating specific climatic factors to treat particular patterns of depression. Most focused on temperature, believing, like Aristotle, that heat elevates mood. For example, Esquirol (9) wrote that “heat, like cold, acts upon the insane, with this difference, that the continuance of warmth augments the excitement, while cold prolongs the depression” (p. 31).

An opposite opinion was held by Soranus and Caelius Aurelianus and other physicians of the “Solidist” school (53), who argued that “mania is aggravated and intensified . . . by cooling remedies” (p. 29), and Kraepelin (54) appears to have agreed with this view. In preliminary studies, Wehr et al. (20, 26) reported that exposure to cold improved summer depression in some patients and that exposure to heat induced depressive symptoms.

The idea that light and darkness can influence depression also has ancient origins. Greek and Roman physicians conceived of depression as a kind of internal darkness (4). In the second century, Galen, citing Hippocrates, wrote that “the color of the black humor induces fear when its darkness throws a shadow over the area of thought . . . as external darkness renders almost all persons fearful” (4, p. 42). This idea was still in vogue 1,400 years later when Thomas Willis wrote that the animal spirits “become in melancholy obscure, thick, and dark, so that they represent the images of things, as it were, in a shadow or covered with darkness” (4, p. 111).

Remarkably, light was used to treat depression and lethargy nearly 2,000 years ago. In the second century, Aretaeus (55) wrote that “lethargics are to be laid in the light, and exposed to the rays of the sun (for the disease is gloom)” (p. 387), and Caelius Aurelianus (56) specified that the light must be applied to the eyes to be effective. Wehr et al. (45) recently confirmed the latter in an experiment. “This light,” said Caelius Aurelianus (56), “may be a lamplight or daylight but should be skillfully arranged, so that . . . it will cover only the patient’s face” (p. 42).

In the modern era, journeys to polar regions led to new insights about a possible connection between light deficiency and depression. Jefferson (57) cited I. Cameron in stating that Frederick Cook, a ship’s physician, recorded that members of an 1898 Antarctic expedition were afflicted with “langour” during the winter darkness and that “bright artificial lights relieve this to some extent.” To our knowledge, the first report of phototherapy of winter depression in a medical journal was written by Marx in 1946 (34). Marx described episodes of recurrent winter depression among soldiers in northern Scandinavia and reported that he successfully treated them with light. He speculated that the condition was due to hypophyseal insufficiency caused by light deprivation and that the therapeutic effects of light were mediated by retinohypophyseal pathways.

A patient who suffered from regularly recurring winter depressions played an important role as a catalyst of modern phototherapy research. He thought that seasonal changes in light might be responsible for his mood swings. When he learned of the research on human melatonin at the National Institute of Mental Health (NIMH) (58), he consulted the researchers about his illness. Animal researchers (59–61) had already demonstrated that light triggers seasonal changes in reproduction and that its effects are mediated by suppression of pineal melatonin secretion. Because the NIMH group had shown that human melatonin secretion could be suppressed by bright light (58) and had speculated that light acting on seasonal photoperiodic mechanisms might have antidepressant effects (62, 63), Lewy et al. (58) proposed to the patient that they treat his winter depression with bright light. He was treated during the winter and improved (21). In that same winter, Mueller, whom the patient

had consulted, also successfully treated a patient with light (2, 36).

In 1984, Rosenthal et al. (2) reported controlled trials of phototherapy of winter depression conducted in 1982. These trials used sham treatments, blind raters, and balanced randomization crossover designs and showed that bright light was an effective antidepressant in most patients. Subsequently, investigators at 15 different research centers in the United States and Europe conducted similar trials and replicated these findings. These studies have revealed a great deal about effective phototherapy.

LIGHT THERAPY OF WINTER DEPRESSION

A recent review by Rosenthal et al. (64) of controlled studies of phototherapy found that these studies demonstrated that bright light is a rapid and effective treatment for winter depression (2, 22, 23, 35, 37–39, 41–49, 51). Using treatment response criteria of a 50% reduction in Hamilton depression rating scores and a final score of less than 8, Terman et al. (51) noted that 40%–50% of patients improved after a week of treatment with bright light. According to the studies, relapse occurs equally rapidly after treatment is discontinued. Only about 10% of patients respond to light of lower intensity, which has been used as a control treatment in a number of the studies.

Investigators have evaluated the importance of several characteristics of phototherapy, including its intensity, duration, timing, spectral qualities, and anatomical route of administration.

The intensity of light appears to influence patients' responses to phototherapy. In crossover studies with blind raters, Rosenthal et al. (2, 35) established that bright light treatment (2,500 lux) is significantly superior to dim light treatment (300 lux or less), and this finding has been replicated by several other groups (22, 42, 43, 49). Recently, Terman (28) showed that 10,000 lux is significantly superior to 2,500 lux and is effective when used for only 30 minutes per day.

The results of some studies suggest that the response to phototherapy is proportional to its total daily duration. Wirz-Justice et al. (46) found that 2 hours of light treatment were superior to half an hour, and Terman et al. (51) found that 4 hours were superior to 2 and that 2 hours were superior to 1. In comparisons among studies (37, 39, 41, 43, 45, 51), the patients who failed to improve after evening phototherapy had received the shortest durations of treatment. On the other hand, Lewy et al. (39) found no difference between 2 hours and half an hour of treatment. In the previously mentioned study of Terman (28), half an hour of 10,000 lux exposure was as effective as 2 hours of 2,500 lux, suggesting that there may be a reciprocal interaction of duration and intensity in patients' responses to phototherapy. Brief, high-intensity light treatments are much easier to schedule than the longer, dimmer light treatments that have been used in

most studies. If such treatments prove to be safe and effective, phototherapy could become more convenient and practical.

It is unclear how important it is to treat patients with seasonal affective disorder at a particular time of day. Several investigators (39, 41, 47, 51) found that morning treatments were superior to evening treatments, and Terman et al., in a cross-center analysis (28), concluded that adding evening to morning light treatment did not improve efficacy. However, Hellekson et al. (37), Yerevanian et al. (38), and Wirz-Justice et al. (50) found no difference between morning and evening treatments, and there is considerable evidence that treatments are effective when they are administered in the morning (22, 37, 39, 41, 48, 51; unpublished paper of Avery et al.), the evening (37, 43, 45, 51), the morning plus the evening (2, 22, 23, 35, 37, 38, 41, 42), or during daylight hours (44, 48, 49). Thus, the timing of treatments does not appear to be critical for most patients, although morning treatments appear to be relatively more effective than evening treatments, and some patients respond only to morning treatments (51).

Only one controlled study has specifically addressed the question of the anatomical route through which light exerts its antidepressant effects. Wehr et al. (45) compared the effects of skin versus eye exposure to light in 10 patients with winter depression and found eye exposure to be significantly more effective.

So far, little is known about which wavelengths of light are responsible for its antidepressant effect. Most investigators have used full-spectrum fluorescent light in their studies. These lights resemble other fluorescent lights but have more blue and near-ultraviolet light and less yellow and green light. However, results of three separate studies (39, 51; unpublished 1989 paper of Frank et al.) indicate that light need not contain ultraviolet rays to be effective. In view of the potential toxicity of ultraviolet light, this is an important finding. However, since one group (unpublished 1989 paper of Frank et al.) found that ultraviolet light appeared to be necessary for amelioration of a specific subset of depressive symptoms, the issue deserves further study.

As with any other treatment, it is important to control for the placebo effect in studies of phototherapy. However, since phototherapy cannot be concealed from the patient, it may never be possible to do so effectively. An important element of the placebo effect is the patient's expectations before treatment. Investigators have attempted to deal with this problem by devising plausible control treatments and evaluating expectations of both active and control treatments (37, 39, 43). Control treatments have included light sources of different intensities (2, 22, 35, 42, 43, 45, 49) and spectra (2, 42), light administered at different times of day (23, 37–39, 41, 44, 50, 51; unpublished paper of Avery et al.) and for different durations (22, 41, 49), and light presented in different ways to the patient, for example, to the skin as opposed to the eyes (45). Not-

withstanding all of these efforts, however, it is unlikely that the problem of the placebo effect has been definitively addressed in any of the studies (45). The same can be said of many studies of drug treatment of depression (65).

Taken together, these findings suggest guidelines for phototherapy of winter depression. Patients' eyes should be exposed to diffused visible light. The light should be sufficiently intense and the treatments sufficiently long (e.g., 2,500 lux for at least 2 hours). Treatments should be administered every day throughout the seasonal period of risk. Morning treatments are preferable, although evening treatments may also be effective in many cases.

O'Rourke et al. (personal communication) found that winter depression responded to treatment with *d*-fenfluramine. Our clinical experience leads us to believe that patients with seasonal affective disorder can be treated successfully with conventional antidepressant drugs. Furthermore, drugs and phototherapy appear to be synergistic in their effects.

THE MECHANISM OF LIGHT THERAPY

Three hypotheses have been advanced to explain the antidepressant effects of phototherapy: the melatonin hypothesis, the circadian rhythm phase shift hypothesis, and the circadian rhythm amplitude hypothesis. All three hypotheses involve effects of light on different characteristics of circadian rhythms.

According to the melatonin hypothesis (2, 44), which was inspired by animal studies of seasonal rhythms (59–61), changes in the length of the day (photoperiod) trigger winter depression by modifying the pattern of nocturnal melatonin secretion, which acts as a chemical signal of darkness. According to this model, phototherapy should be effective only when it is administered before dawn or after dusk, thus interrupting the long winter night and abbreviating the phase of active melatonin secretion. Phototherapy should be ineffective when it is administered after dawn and before dusk, leaving the photoperiod and the pattern of melatonin secretion unchanged.

Experimental evidence does not provide strong support for the melatonin hypothesis. Light administered during daylight hours is an effective antidepressant even though it does not extend the photoperiod and does not modify the pattern of nocturnal melatonin secretion (44, 48). Restoring high plasma levels of melatonin during light treatments by administering melatonin to individuals who have responded to phototherapy only partially reverses the antidepressant effect of light (66). Finally, atenolol, a β -adrenergic antagonist drug that, like light, suppresses melatonin secretion, does not clearly improve winter depression in most patients (67).

According to the circadian rhythm phase shift hypothesis, winter depression occurs when the circadian rhythm phases become abnormally delayed relative to

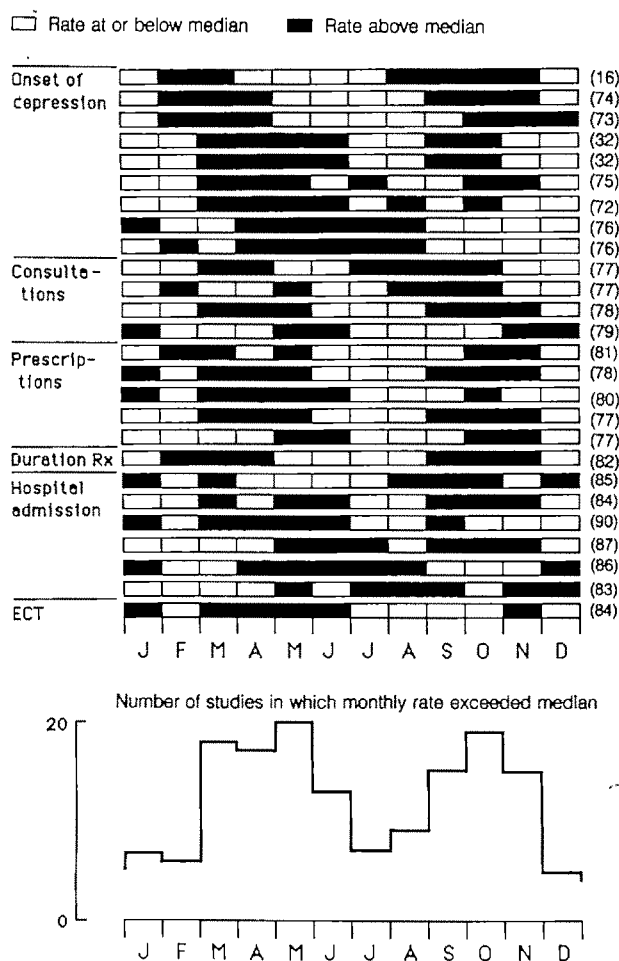
sleep because dawn comes later. Since morning light advances and evening light delays the phase position of circadian rhythms, morning light should improve winter depression and evening light should have the opposite effect. In support of this hypothesis, Lewy et al. (39) published evidence that 1) the circadian rhythm phase in melatonin secretion is abnormally delayed in patients with winter depression, 2) morning light advances and evening light delays phase position, and 3) morning light is a more effective treatment than evening light. The last finding is also supported by results of Terman et al. (41) and unpublished results of Avery et al. However, some investigators (37, 51) have failed to show a significantly superior effect of morning versus evening light, abnormally phase-delayed circadian rhythms, or a phase-shifting effect of phototherapy in winter depression (68). Furthermore, other investigators (37, 43, 45, 51) have shown that phototherapy administered in the evening, which ought to worsen depression according to the hypothesis, improves it instead. Nevertheless, the hypothesis continues to receive some support, and it appears to deserve further investigation.

According to the circadian rhythm amplitude hypothesis, winter depression is caused by a reduction in the amplitude of circadian rhythms and phototherapy improves winter depression by increasing the amplitude of circadian rhythms (69). Light influences the amplitude of circadian rhythms, and, as with phase resetting, the timing of its administration determines the magnitude and direction of its effect (69). Since light in the middle of the day increases circadian rhythm amplitude and light in the middle of the night decreases amplitude, light in the middle of the day ought to restore a normal amplitude and improve winter depression. Consistent with this hypothesis, there is considerable evidence that amplitudes of circadian rhythms are abnormally low in depression in general (69), and there is some evidence that they are low in winter depression in particular (68). However, the amplitude hypothesis has not yet been tested in an experiment.

SEASONAL INFLUENCES ON AFFECTIVE ILLNESS IN GENERAL

Epidemiologic and clinical studies suggest that two different seasonal influences may operate on several phenomena relevant to affective disorders—suicide rates (70–72), onset of affective episodes (16, 18, 32, 72–76), first visits to a physician for treatment of depression (77–79), first prescriptions of antidepressant medications (77, 79–81), time lags for antidepressant response (82), rates of placebo response to antidepressants (28), hospital admissions for depression (83–88; however, see 89–91), and ECT (84) (see figure 3). For all these phenomena, most studies find two seasonal peaks, one in spring and one in fall.

Data on suicide are extensive and have been well reviewed elsewhere (70, 71). Most studies consistently found an increase in suicides in the late spring and

FIGURE 3. Monthly Rates of Onset and Treatment of Depressive Episodes Reported in the Literature^a

^aFor each study the months whose rates exceeded the median monthly rate (usually 6) for the year or whose rates matched or were lower than the median monthly rate for the year are given. The numbers on the right side of the diagram indicate the references for the studies. The histogram in the lower part of the figure summarizes the results of all of the studies by showing for each month the number of studies in which the monthly rate exceeded the median for the year. Spring (March, April, and May) and fall (September, October, and November) peaks were the most common pattern.

^bUnipolar.

^cBipolar.

^d1983.

^e1984.

early summer. About one-third of the studies also found a second, smaller peak in the fall and early winter. Thus, the times of the year when summer depression and winter depression begin correspond to the times of the year when the risk for suicide in the general population is greatest.

A number of investigators have studied seasonal patterns in the onset of episodes of depression in patients with affective disorders not specifically identified as seasonal affective disorder. Most found robust seasonal patterns in the onset of depressive episodes with

both spring peaks (as in the onset of summer depression) and fall peaks (as in the onset of winter depression) (figures 1 and 3). We found eight studies that examined month of onset of depressive episodes in a total of 11 patient groups. Data for some manic episodes may have been combined with data for depressive episodes for bipolar patients in one study (32) and for unipolar plus bipolar patients in another (72). Altogether, 4,667 episodes in approximately 2,400 patients were investigated. In each study, investigators found a spring peak in March (16, 18, 73), April (32, 74), or May (32, 72, 75, 76) and a fall peak in September (16, 72), October (18, 32, 75), or November (73, 74). One study (76) found a winter peak in January; also see (19). In one study (32) the average duration of depressive episodes was similar to that observed in seasonal affective disorder (figure 1).

Summer and winter depressions in patients with seasonal affective disorder begin in the spring and fall, respectively. In the studies cited the seasonal patterns of onset of depression are not precisely identical, but they appear to be rather similar to those in seasonal affective disorder (figures 1 and 3). How might this similarity be explained?

Since seasonal affective disorder has been reported to occur in between 16% and 38% of patients with recurrent depression (24, 28, 29), it is possible that the seasonal pattern observed in patients with general affective disturbances represents the behavior of subgroups of patients with seasonal affective disorder. The times of onset of seasonal affective disorder (both winter and summer types) correspond fairly well to the seasonal patterns of onset found in studies of patients with depressive disorders not identified as seasonal affective disorder (figures 1 and 3). Further, in one of these studies (32), the mean duration of depressive episodes resembled that found in seasonal affective disorder (figure 1).

An alternative explanation is that even in patients whose affective episodes are not predictably seasonal, there is a seasonal variation in affective vulnerability. Thus, they are more likely to experience depressions at certain times of the year under the influence of certain climatic variables. Fifty years ago, Slater (72) reviewed the patterns of recurrence of illness in affective patients diagnosed by Kraepelin and observed a tendency for affective episodes to occur at the same time of the year for the same individuals. Unfortunately, this promising line of investigation has not been pursued further.

As we have noted, the clinical pictures of regular summer and winter depressions are reminiscent of endogenous and atypical subtypes described in groups of patients with depressive disorders. Such observations might be compatible with reports from Ontario by Eastwood and Peacocke (84) and Eastwood and Stiasny (88), who found that hospital admissions for endogenous and neurotic depression peaked in spring and fall, respectively, and that the administration of ECT treatments occurred most commonly in spring.

One of the implications of many of the cited studies

is that the occurrence of depressive episodes in patients without seasonal affective disorder may be influenced to a certain extent by the same environmental factors that appear to be responsible for the recurrences of episodes in patients with seasonal affective disorder. This interpretation raises the possibility that manipulations of the physical environment might prove to be more generally useful as treatments for affective illness. In this regard, a few reports (92–95) have suggested that depressions not specifically identified as seasonal may respond to phototherapy. However, these reports are preliminary, and the question needs to be investigated further.

POSSIBLE IMPLICATIONS OF SEASONALITY

The seasonality of some forms of affective illness and their sensitivity to environmental factors may be clues to the nature of affective illness: it might be a disorder of systems that mediate the organism's adaptations to changes in the physical environment.

Consistent with this hypothesis is the fact that, as Lange observed 60 years ago (96), many animals, in their normal adaptations to changes in the physical environment, exhibit behavioral and physiological adjustments that are similar in kind and degree to those exhibited by manic and depressed patients. For example, at different times of the year animals eat more or less, gain or lose weight, become active or lethargic, sleep more or less, become more or less interested in sex, and interact more or less with their physical and social environment (59–61).

There are also many parallels between the time course of these changes in animals and the time course of changes in patients with affective disorders. Both sets of changes are reversible and recurrent and may recur episodically or cyclically. Cyclic recurrences can be synchronized with seasonal cycles in the environment or can become independent of seasonal cycles (for example, when animals are removed from their natural environment) (97). Both sets of changes can be precipitated, sometimes quite rapidly, by changes in environmental factors such as light and temperature.

These changes in animals should not be taken too literally as models of affective illness, but we believe that an understanding of their biological function might help to explain the nature of affective illness. In spite of their diversity, many of these changes in animals can be understood as strategies for managing the energy economy of the organism in the face of changing external challenges to energy balance (98). Environmental factors that affect the energy economy of animals most directly are the availability of food and the ambient temperature. Some of the variations in these factors are associated with daily and seasonal cycles in the environment and are therefore predictable. As an adaptation to these predictable changes, animals have evolved circadian and seasonal rhythms that program changes in energy balance in such a way

as to anticipate changes connected with environmental cycles and to maximize the efficiency of energy use (99). These rhythms are synchronized with corresponding cycles in the environment by changes in ambient light and other factors.

The hypothalamus is the focal point of a neural network that integrates the actions of energy balance mechanisms and coordinates them with changes in the environment. Through nerves and humoral factors, the hypothalamus monitors and regulates exposure to external factors such as light, temperature, and nutrients that affect energy balance. The hypothalamus also monitors and regulates physiological systems and behaviors that help to control energy balance, such as appetite, metabolism, weight, physical activity, the drive to interact with the physical and social environment, sleep, and body temperature. The autonomic nervous system, the hypothalamic-pituitary-adrenal axis, and the hypothalamic-pituitary-thyroid axis, all of which have been implicated in affective illness, are important mediators of energy homeostasis (100). The hypothalamus also regulates and coordinates the timing of changes in these factors through pacemakers that generate daily and seasonal rhythms (62, 99). If affective illness is a disorder of the network of physiological systems that regulates energy balance, then it is probably these structures which are affected.

In certain animals, light can regulate activity and sleep in ways that resemble the effects of phototherapy on winter depression. When diurnal animals live in constant light, increasing the intensity of the light causes them, like patients with winter depression when they are treated with phototherapy, to sleep less and become more active (101). These effects of light on animals are mediated by retinohypothalamic pathways that modify the behavior of the hypothalamic pacemaker that controls daily cycles in activity and sleep. Homologous neural mechanisms appear to be present in the human brain, and they might mediate the effects of phototherapy on activity and sleep in patients with seasonal affective disorder.

CONCLUSIONS

To the modern psychiatrist, recent reports about the influence of seasons and the physical environment on affective illness might appear novel and relevant only to a few, unusual patients. However, for 2,400 years seasonal and environmental influences have been enduring themes in writings on depression and mania and have played a significant role in theories of pathogenesis and treatment. This historical record is consistent with modern observations about seasonality.

Modern psychiatrists seem to be much less aware than their predecessors of the seasonality of affective illness and its implications regarding environmental causes. Ironically, one version of the widely used Hamilton Rating Scale for Depression (102) contains

instructions to rate patients as lacking insight into their illness if they attribute their depression to climate.

Modern psychiatrists' lack of interest in seasonality could be attributed to several factors. First, theories play an important role in medicine, and the ancient humoral theory that emphasized seasonal influences on disease has fallen into disfavor. Second, theories of seasonality were replaced long ago by psychological and biological theories that emphasize internal mental and biochemical processes, respectively. These theories dominated psychiatric thinking for most of this century. Third, during the past several hundred years belief in the idea of progress has increasingly altered the way we view the world, causing a cultural shift away from a cyclical to a linear perception of time (103). For this reason, modern psychiatrists and patients may be more likely than their predecessors to perceive affective recurrences as a succession of unique events rather than a seasonal cycle of events. Fourth, although Kraepelin (15) made an enormous contribution in classifying mental illness according to longitudinal course and separating the recurrent mood disorders from schizophrenia, he took a different view of such an approach within the mood disorders themselves, noting that all attempts to classify subtypes of affective illness on the basis of their course "must of necessity wreck on the irregularity of the disease" (p. 139). The usefulness of separating patients with seasonal recurrences because of their responsiveness to phototherapy suggests that Kraepelin may have been incorrect in this regard. Finally, modern treatments of affective illness may have altered its course (104, 105), thereby obscuring seasonal influences.

Seasonal influences on depression and mania appear to merit the attention of psychiatrists who treat affective disorders. Seasonal affective disorder does not appear to be uncommon in the general population and in clinics specializing in the treatment of affective disorders. Furthermore, factors that trigger summer and winter depressions might also be risk factors for suicide and depression.

Clearly, there is a need for further research on these issues. The renewal of interest in the seasonality of affective illness has already led to an effective non-pharmacological treatment, phototherapy, and it seems likely to provide further insights into the nature and causes of the illness.

REFERENCES

1. Hippocrates: On Endemic Diseases (Air, Waters and Places), vol 5. Edited by Mattock JN, Lyons MC. Cambridge, Heffer & Sons, 1969
2. Rosenthal NE, Sack DA, Gillin JC, et al: Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry* 1984; 41:72-80
3. Garfield E: Current research on seasonal affective disorder and phototherapy. *Current Contents Life Sciences* 1988; 31:3-9
4. Jackson SW: Melancholia and Depression From Hippocratic Times to Modern Times. New Haven, Yale University Press, 1987

5. Hippocrates: Aphorisms, in Hippocrates IV. Translated by Jones WHS. Cambridge, Harvard University Press, 1959
6. Roccatagliata G: A History of Ancient Psychiatry. New York, Greenwood Press, 1986
7. Aristotle: Problemata, book XXX, problem 1, in The Works of Aristotle Translated Into English, vol VII. Edited by Ross WD; translated by Forster ES. Oxford, Oxford University Press, 1953
8. Pinel P: A Treatise on Insanity. Translated by Davis DD. London, Cadell and Davies, 1806
9. Esquirol JED: Mental Maladies: Treatise on Insanity. Translated by Hunt EK. Philadelphia, Lea & Blanchard, 1845
10. Dewhurst K: A seventeenth-century symposium on manic-depressive psychosis. *Br J Med Psychol* 1962; 35:113-125
11. Philips E: The life of Mr John Milton (1694), in The Student's Milton. Edited by Patterson FA. New York, Appleton-Century-Crofts, 1957
12. Griesinger W: Mental Pathology and Therapeutics (1855). Translated by Robertson CL, Rutherford J. New York, William Wood, 1882
13. Baillarger J: Note sur une genre de folie dont les accès sont caractérisés par deux périodes régulières, l'une de dépression et l'autre d'excitation. *Gazette Hebdomadaire de Médecine et Chirurgie* 1854; 132:263-265
14. Pilcz A: Die periodischen Geistesstörungen. Jena, G Fischer Verlag, 1901
15. Kraepelin E: Manic-Depressive Insanity and Paranoia. Translated by Barclay RM; edited by Robertson GM. Edinburgh, E & S Livingston, 1921
16. Kraines S: Mental Depressions and Their Treatment. New York, Macmillan, 1957
17. Mayer-Gross W, Slater E, Roth M: Clinical Psychiatry, 2nd ed. London, Cassell, 1960
18. Matussek P, Halbach A, Troeger U: Endogene Depression. Munich, Urban & Schwarzenberg, 1965
19. Kinkelin M: Verlauf und Prognose des manisch-depressiven Irreseins. *Schweiz Arch Neurol Psychiatr* 1954; 73:100-140
20. Wehr TA, Sack DA, Rosenthal NE: Seasonal affective disorder with summer depression and winter hypomania. *Am J Psychiatry* 1987; 144:1602-1603
21. Lewy AJ, Kern HA, Rosenthal NE, et al: Bright artificial light treatment of a manic-depressive patient with a seasonal mood cycle. *Am J Psychiatry* 1982; 139:1496-1498
22. Wirz-Justice A, Buchelli C, Graw P, et al: Light treatment of seasonal affective disorder in Switzerland. *Acta Psychiatr Scand* 1986; 74:193-204
23. Thompson C, Isaacs G: Seasonal affective disorder—a British sample: symptomatology in relation to mode of referral and diagnostic subtype. *J Affective Disord* 1988; 14:1-11
24. Garvey MJ, Wesner R, Godes M: Comparison of seasonal and nonseasonal affective disorders. *Am J Psychiatry* 1988; 145:100-102
25. Boyce P, Parker G: Seasonal affective disorder in the southern hemisphere. *Am J Psychiatry* 1988; 145:96-99
26. Wehr TA, Giesen HA, Schulz PM, et al: Summer depression: description of the syndrome and comparison with winter depression, in Seasonal Affective Disorder and Phototherapy. Edited by Rosenthal NE, Blehar M. New York, Guilford Press, 1989
27. Kasper S, Wehr TA, Bartko J, et al: Epidemiological findings of seasonal changes in mood and behavior: a telephone survey of Montgomery County, Maryland, USA. *Arch Gen Psychiatry* (in press)
28. Terman M: On the question of mechanism in phototherapy: considerations of clinical efficacy and epidemiology. *J Biol Rhythms* 1988; 3:155-172
29. Thase M: Defining and treating seasonal affective disorder. *Psychiatr Annals* 1986; 16:733-737
30. Montplaisir J: Sleep in depression, schizophrenia, and narcolepsy, in The Bio-Clinical Interface: Sleep and Psychiatry. Edited by Macher J-P, Crocq M-A. Basel, Aesopus (in press)
31. Kasper S, Rogers S, Yancey A, et al: Phototherapy in individ-

- uals with and without subsyndromal seasonal affective disorder. *Arch Gen Psychiatry* (in press)
32. Angst J, Grof P, Hippus H, et al: La psychose manico-dépressive est-elle périodique ou intermittente? in *Cycles Biologiques et Psychiatrie* (Symposium Bel-Air). Geneva, Masson, 1968
 33. Davidson JRT, Miller RD, Turnbull CD, et al: Atypical depression. *Arch Gen Psychiatry* 1982; 39:527-534
 34. Marx H: "Hypophysäre Insuffizienz" bei Lichtmangel. *Klin Wochenschr* 1946; 24/25:18-21
 35. Rosenthal NE, Sack DA, Carpenter CJ, et al: Antidepressant effects of light in seasonal affective disorder. *Am J Psychiatry* 1985; 142:163-170
 36. Mueller PS, Allen NG: Diagnosis and treatment of severe light-sensitive seasonal energy syndrome (SES) and its relationship to melatonin anabolism. *Fair Oaks Hospital Psychiatry Letter* 1984; 2:1-5
 37. Hellekson CJ, Kline JA, Rosenthal NE: Phototherapy for seasonal affective disorder in Alaska. *Am J Psychiatry* 1986; 143:1035-1037
 38. Yerevanian BI, Anderson JL, Grota LJ, et al: Effects of bright incandescent light on seasonal and non-seasonal major depressive disorder. *Psychiatry Res* 1986; 18:355-364
 39. Lewy AJ, Sack RL, Miller LS, et al: Antidepressant and circadian phase-shifting effects of light. *Science* 1987; 235:352-354
 40. Sonis WA, Yellin AM, Garfinkel BD, et al: The antidepressant effect of light in seasonal affective disorder in childhood and adolescence. *Psychopharmacol Bull* 1987; 23:360-363
 41. Terman M, Quitkin FM, Terman JS, et al: The timing of phototherapy: effects on clinical response and the melatonin cycle. *Psychopharmacol Bull* 1987; 23:354-357
 42. Checkley S, Winton F, Franey C, et al: Antidepressant effects of light in seasonal affective disorder, in *Seasonal Affective Disorder*. Edited by Silverstone T, Thompson C. London, CNS Clinical Neuroscience (in press)
 43. James SP, Wehr TA, Sack DA, et al: Treatment of seasonal affective disorder with light in the evening. *Br J Psychiatry* 1985; 147:424-428
 44. Wehr TA, Jacobsen FM, Sack DA, et al: Phototherapy of seasonal affective disorder: time of day and suppression of melatonin are not critical for antidepressant effects. *Arch Gen Psychiatry* 1986; 43:870-875
 45. Wehr TA, Skwerer RG, Jacobsen FM, et al: Eye versus skin phototherapy of seasonal affective disorder. *Am J Psychiatry* 1987; 144:753-757
 46. Wirz-Justice A, Schmid AC, Graw P, et al: Dose relationships of morning bright white light in seasonal affective disorders (SAD). *Experientia* 1987; 43:574-576
 47. Lewy AJ, Sack RL, Singer CM, et al: The phase shift hypothesis for bright light's therapeutic mechanism of action: theoretical considerations and experimental evidence. *Psychopharmacol Bull* 1987; 23:349-353
 48. Jacobsen FM, Wehr TA, Skwerer RA, et al: Morning versus midday phototherapy of seasonal affective disorder. *Am J Psychiatry* 1987; 144:1301-1305
 49. Isaacs G, Stainer DS, Sensky TE, et al: Phototherapy and its mechanism of action in seasonal affective disorder. *J Affective Disord* 1988; 14:13-19
 50. Wirz-Justice A, Graw P, Kräuchi K, et al: Phototherapy in Switzerland: "Mehr Licht," in *Seasonal Affective Disorder*. Edited by Silverstone T, Thompson C. London, CNS Clinical Neuroscience (in press)
 51. Terman M, Terman JS, Quitkin FM, et al: Light therapy for seasonal affective disorder: a review of efficacy. *Neuropsychopharmacology* (in press)
 52. Hippocrates: Regimen in health, in *Hippocrates IV*. Translated by Jones WHS. Cambridge, Harvard University Press, 1959
 53. Classic descriptions of psychopathology: Soranus of Ephesus and Caelius Aurelianus (fifth century), Rome, in *Documentary History of Psychiatry: A Source Book on Historical Principles*. Edited by Goshen CE. New York, Philosophical Library, 1967
 54. Defendorf AR: *Clinical Psychiatry, a Text-Book for Students and Physicians Abstracted and Adapted From the Sixth German Edition of Kraepelin's "Lehrbuch der Psychiatrie."* New York, Macmillan, 1902
 55. On the therapeutics of acute diseases, in *The Extant Works of Aretaeus, the Cappadocian*. Edited and translated by Adams F. London, Sydenham Society, 1856
 56. Caelius Aurelianus: On Acute Diseases and on Chronic Diseases. Edited and translated by Drabkin EI. Chicago, University of Chicago Press, 1950
 57. Jefferson JW: An early study of seasonal depression (letter). *Am J Psychiatry* 1986; 143:261-262
 58. Lewy AJ, Wehr TA, Goodwin FK, et al: Light suppresses melatonin secretion in humans. *Science* 1980; 210:1267-1269
 59. Gwinner E: Annual rhythms: perspective, in *Handbook of Behavioral Neurobiology*, vol 4. Edited by Aschoff J. New York, Plenum, 1981
 60. Hoffman K: Photoperiodism in vertebrates. *Ibid*
 61. Goldman B, Darrow J: The pineal gland and mammalian photoperiodism. *Neuroendocrinology* 1983; 37:386-396
 62. Wehr TA, Goodwin FK: Biological rhythms and psychiatry, in *American Handbook of Psychiatry*, vol VII. Arieti S, editor-in-chief. New York, Basic Books, 1981
 63. Kripke DF, Mullaney DJ, Atkinson M, et al: Circadian rhythm disorders in manic-depressives. *Biol Psychiatry* 1978; 13:335-350
 64. Rosenthal NE, Sack DA, Skwerer RG, et al: Phototherapy for seasonal affective disorder. *J Biol Rhythms* 1988; 3:101-120
 65. Hughes JR, Krahn D: Blindness and the validity of the double-blind procedure. *J Clin Psychopharmacol* 1985; 5:138-142
 66. Rosenthal NE, Sack DA, Jacobsen FM, et al: Melatonin in seasonal affective disorder and phototherapy. *J Neural Transm (Suppl)* 1986; 21:257-267
 67. Rosenthal NE, Jacobsen FM, Sack DA, et al: Atenolol in seasonal affective disorder: a test of the melatonin hypothesis. *Am J Psychiatry* 1988; 145:52-56
 68. Skwerer RG, Jacobsen FM, Duncan CC, et al: Neurobiology of seasonal affective disorder and phototherapy. *J Biol Rhythms* 1988; 3:135-154
 69. Czeisler CA, Kronauer RE, Mooney JJ, et al: Biologic rhythm disorders, depression, and phototherapy: a new hypothesis. *Psychiatr Clin North Am* 1987; 10:687-709
 70. Faust V, Sarreither P: Jahreszeit und psychiatrische Krankheit. *Med Klin* 1975; 70:467-473
 71. Aschoff J: Annual rhythms in man, in *Handbook of Behavioral Neurobiology*, vol 4: Biological Rhythms. Edited by Aschoff J. New York, Plenum, 1981
 72. Slater E: Zur Periodik des manisch-depressiven Irreseins. *Ztschr Neurol Psychiatr* 1938; 162:794-801
 73. Strzyzewski W, Nowakowska C: [The role of triggering factors in the pathogenesis of depressive syndromes.] *Psychiatr Pol* 1983; 17:31-37 (Polish)
 74. Payk TR: [Seasonal relationship between neurologic and psychiatric diseases.] *MMW* 1976; 118:1669-1670 (German)
 75. Leuthold GH: Jahreszeit und Phasenbeginn manisch-depressiver Psychosen. *Arch Psychiatr* 1940; 111:55-61
 76. Frangos E, Athanassenas G, Tsitourides S, et al: Seasonality of the episodes of recurrent affective psychoses: possible prophylactic interventions. *J Affective Disord* 1980; 2:239-247
 77. Tansella M, Williams P, Balestrieri M, et al: The management of affective disorders in the community. *J Affective Disord* 1986; 11:73-79
 78. Harris CM: Seasonal variations in depression and osteoarthritis. *J R Coll Gen Pract* 1984; 34:436-439
 79. Harris CM: Further observations on seasonal variation, 2: depression. *J R Coll Gen Pract* 1986; 36:319-321
 80. Skegg K, Skegg DCG, McDonald BW: Is there a seasonal variation in the prescribing of antidepressants in the community? *J Epidemiol Community Health* 1986; 40:285-288
 81. Williams P, Dunn G: Cyclical variation in psychotropic drug prescription. *J Epidemiol Community Health* 1981; 35:136-138
 82. Sedivec V: Influence of the seasons on the course and thera-

- peutic results of depressive phases of maniomelancholy. *Cesk Psychiatr* 1981; 77:326-330
83. Amaldi P: Stati affettivi delle psicosi maniaco-depressive e ritmo stagionale. *Rivista Sperimentale Freniatria* 1928; 53: 461-467
84. Eastwood MR, Peacocke J: Seasonal patterns of suicide, depression and electroconvulsive therapy. *Br J Psychiatry* 1976; 129:472-475
85. Winzenreid FJM: Über langfristige Perioden in der Psychiatrie. *Med Welt* 1965; 10:489-493
86. Abe K: Seasonal fluctuation of psychiatric admissions. *Folia Psychiatr Neurol Jpn* 1963; 17:101-112
87. Hare EH, Walter SD: Seasonal variation in admissions of psychiatric patients and its relation to seasonal variation in their births. *J Epidemiol Community Health* 1978; 32:47-52
88. Eastwood MR, Stiasny S: Psychiatric disorder, hospital admission and season. *Arch Gen Psychiatry* 1978; 35:769-771
89. Parker G, Walter S: Seasonal variation in depressive disorders and suicidal deaths in New South Wales. *Br J Psychiatry* 1982; 140:626-632
90. Zung WWK, Green RL: Seasonal variation of suicide and depression. *Arch Gen Psychiatry* 1974; 30:89-91
91. Massing W, Angermeyer MC: Zur Frage saisonaler Schwankungen in der Manifestation psychischer Erkrankungen. *Arch Psychiatr Nervenkr* 1983; 233:139-150
92. Kripke DF, Mullaney DJ, Gillin JC, et al: Phototherapy of non-seasonal depression, in *Biological Psychiatry 1985: Proceedings of the IVth World Congress of Biological Psychiatry*. Edited by Shagass C, Josiassen RC, Bridger WH, et al. New York, Elsevier, 1986
93. Dietzel M, Saletu B, Lesch OM: Bright light treatment of depressive illness: polysomnographic data-analysis. *Ibid*
94. Peter K, Rübiger U, Kowalik A: Erste Ergebnisse mit Bright-Light (Phototherapie) bei affektiven Psychosen. *Psychiatr Neurol Med Psychol (Leipz)* 1986; 38:384-390
95. Parry BL, Berga SL, Mostofi N, et al: Morning vs evening light treatment of patients with premenstrual depression, in *Abstracts of the American College of Neuropsychopharmacology Meeting*. Nashville, Tenn, ACNP, 1987
96. Lange J: Die endogenen und reaktiven Gemütskrankungen, in *Handbuch der Geisteskrankheiten, Sechster Band*. Edited by Bumke O. Berlin, Springer-Verlag, 1928
97. Mrosovsky N, Melnyk RB, Lang K, et al: Infradian cycles in dormice. *J Comparative Physiology [A]* 1980; 137:315-339
98. Bartholomew CA: Aspects of timing and periodicity of heterothermy, in *Hibernation and Hypothermia: Perspectives and Challenges*. Edited by South FE, Hannon JP, Willis JR, et al. New York, Elsevier, 1972
99. Moore-Ede MC: Physiology of the circadian timing system: predictive versus reactive homeostasis. *Am J Physiol* 1986; 250:R735-R752
100. Bray GA: Autonomic and endocrine factors in the regulation of energy balance. *Fed Proc* 1986; 45:1404-1410
101. Sulzman FM, Fuller CA, Moore-Ede MC: Effects of phasic and tonic light inputs on the circadian organization of the squirrel monkey. *Photochem Photobiol* 1981; 34:249-256
102. Hedlund JL, Vieweg BW: The Hamilton Rating Scale for Depression. *J Operational Psychiatry* 1979; 10:149-165
103. Gould SJ: *Time's Cycle and Time's Arrow: Myth and Metaphor in the Discovery of Geological Time*. Cambridge, Harvard University Press, 1987
104. Wehr TA, Goodwin FK: Can antidepressants cause mania and worsen the course of affective illness? *Am J Psychiatry* 1987; 144:1403-1411
105. Akiskal HS, Mallya G: Criteria for the "soft" bipolar spectrum: treatment implications. *Psychopharmacol Bull* 1987; 23:68-73

Alternatives to Lithium for Preventive Treatment of Bipolar Disorder

Robert F. Prien, Ph.D., and Alan J. Gelenberg, M.D.

The authors review the research literature on drug treatment for the prevention of recurrences in bipolar disorder, emphasizing the available alternatives to lithium therapy. They discuss the need for alternative treatments and the current status of promising agents. Carbamazepine receives special attention because of its status as the most promising backup treatment for lithium. The authors conclude that despite the extensive literature on carbamazepine, there is strong need for carefully designed, prospective, double-blind studies to establish the efficacy of carbamazepine alone and in combination with lithium as a prophylactic treatment for bipolar disorder. Difficulties in developing and evaluating preventive maintenance are discussed.

(Am J Psychiatry 1989; 146:840–848)

The discovery of the effectiveness of lithium in modifying the long-term course of bipolar disorder constitutes one of the major advances in psychiatry. Lithium has been literally a lifesaving treatment for many bipolar patients. A 1979 study on bipolar disorder sponsored by the U.S. Public Health Service (1) estimates that without treatment the average woman experiencing onset of a bipolar disorder at age 25 has a life span 9 years shorter than a 25-year-old woman without the disorder. The report suggests that with adequate treatment (defined as lithium therapy combined with health education about the illness and drug), the 25-year-old woman would recoup 6½ years of life and show substantial improvement in such life activities as work, school, and childrearing. Despite these promising projections, bipolar disorder continues to constitute a serious public health problem. The National Institute of Mental Health epidemiological catchment area study (2) estimates that 0.8% of the adult population in the United States suffers from bipolar I disorder (i.e., a history of depression and at least one manic episode). Had the definition of bipolar

disorder included bipolar II disorder (i.e., a history of hypomania and depression but no mania), the prevalence of bipolar illness would have been considerably higher. Also, patients with bipolar disorder are at high risk for recurrence; a conservative estimate is that over 80% of the individuals who have a manic episode will have one or more recurrences (3). These recurring episodes are not only disruptive and life threatening but often have a progressively deteriorative effect on interepisode functioning and capacity to cope with usual life activities.

We provide an overview of research findings on the preventive treatment of bipolar disorder, emphasizing the current status of alternatives to lithium therapy. The term “preventive treatment” here refers to pharmacologic treatment that is administered over long periods for the purpose of preventing or attenuating recurrences of mania or depression. It is used interchangeably with the more popular term “prophylactic treatment.”

PREVENTIVE THERAPY WITH LITHIUM

Studies comparing lithium to placebo in the preventive treatment of bipolar disorder conclusively demonstrate lithium’s effectiveness in preventing or attenuating recurrences (4–9). In most of the studies, lithium treatment resulted in 50% fewer recurrences than placebo. The studies also demonstrate, however, that lithium is not a panacea for bipolar disorder. The average failure rate for lithium in preventive treatment studies is approximately 33%. In most trials, failure is defined as the appearance of major episodes severe enough to require either hospitalization or psychopharmacologic treatment other than the study medication. Even among lithium responders, only a limited number can expect to achieve complete prevention of episodes. Schou (10) indicates that only about one-fifth of patients who are suitable candidates for lithium treatment can expect to have no recurrences during lithium maintenance treatment; the remaining four-fifths will show varying frequencies and severities of recurrences, ranging from frequent and severe to rare and mild.

Lithium is a particularly poor treatment for patients with a history of rapid cycling (four or more episodes per year) (11–13) or episodes characterized by mixed

Received April 15, 1988; revision received Nov. 8, 1988; accepted Dec. 1, 1988. From the Affective and Anxiety Disorders Research Branch, Division of Clinical Research, NIMH, and the Department of Psychiatry, The Arbour Hospital, Jamaica Plain, Mass. Address reprint requests to Dr. Prien, NIMH, Parklawn Building, Rm. 10C-24, 5600 Fishers Lane, Rockville, MD 20857.

manic and depressive features (14–16). Bipolar patients with personality disturbances also tend to respond poorly to preventive lithium therapy (17, 18). In addition, long-term treatment with lithium may be impeded by such discomforting adverse reactions as weight gain, polyuria, and fine hand tremor, which often lead to noncompliance in taking medication and subsequent relapse. A particularly troublesome problem with lithium is its teratogenic effects (19), which limit its use during pregnancy and demand special caution for women of child-bearing age.

ALTERNATIVES TO LITHIUM THERAPY

The need for alternatives to lithium for the preventive treatment of bipolar disorder has been long recognized. Earlier review articles by Prien (20), Ayd (21), and Lerer (22) stress the need for alternatives not only for long-term treatment but also for acute mania and bipolar depression. However, attempts to provide alternative treatments of established efficacy and safety have met with a number of difficulties.

Paradoxically, the demonstration of lithium's efficacy in the preventive treatment of bipolar disorder has slowed the development of alternative treatments. After lithium was approved by the Food and Drug Administration (FDA) for the preventive maintenance treatment of manic-depressive disorder in 1974, the use of a placebo in evaluating new treatments for the disorder was regarded as unethical by most investigators and Institutional Review Boards. Without the option of conducting a placebo-controlled study, investigators have had to establish the efficacy of a promising agent by comparing it to lithium. The sample size required to attain sufficient statistical power for a drug-drug comparison is beyond the reach of most investigators.

A second difficulty in developing alternatives to lithium is that many university medical centers with the research resources to conduct large-scale maintenance trials tend to see a preponderance of difficult-to-treat patients who have failed to respond to traditional therapeutic approaches in the community. These patients may manifest rapid cycling, substantial impairment in interepisode function, substance abuse, noncompliance in taking medication, concomitant medical disorders, and other complications that can pose severe management problems in conducting a long-term treatment study.

A third problem in the search for an effective alternative is that bipolar disorder has not been a focus for drug development by the pharmaceutical industry. Bipolar disorder is too prevalent to qualify for the Orphan Drug Act but not prevalent enough to attract the interest of pharmaceutical companies. Individual investigators evaluating experimental agents or new indications for established compounds cannot provide the massive scale of research that can be marshaled by a commercial company. This is a serious disadvantage when it is necessary to confirm early claims of efficacy

and safety with large-sample double-blind studies. Because of the considerable expense, sample size requirements, and staff resources needed to conduct well-controlled studies, it is possible that no single center is capable of mounting a definitive maintenance trial and that some collaborative effort involving two or more centers will be required.

Anticonvulsants

Carbamazepine. The anticonvulsants have emerged as the leading alternative to lithium. Of these, carbamazepine is the most extensively studied. Because carbamazepine is regarded by many clinicians as the most promising backup for lithium for preventive treatment (23), we give it special attention in this review.

Carbamazepine has a molecular structure resembling that of imipramine and was synthesized for its potential antidepressant effect. However, animal studies demonstrated promising anticonvulsant properties, and the drug became a widely accepted treatment for patients with trigeminal neuralgia and seizure disorders, particularly temporal lobe epilepsy. Open trials in Japan in the early 1970s (24, 25) raised the possibility that carbamazepine had antimanic and prophylactic effects in manic-depressive patients. There were also reports that the use of carbamazepine as an anticonvulsant in epileptic patients produced psychiatric improvement (26). These findings led to more systematic studies of the effectiveness of the drug in mood disorders, especially for bipolar patients.

In a 1986 review, Post et al. (27) examined 16 trials that provided data on the preventive efficacy of carbamazepine in bipolar disorder. Of the 257 patients studied, approximately two-thirds were rated as showing some improvement after treatment with carbamazepine alone or in combination with lithium or other medications. The majority of the studies were uncontrolled clinical trials or case presentations. However, Post et al. indicated that the findings from the controlled and uncontrolled studies were similar. They concluded that the evidence supports the efficacy of carbamazepine in the long-term maintenance treatment of bipolar patients and that carbamazepine is especially effective for patients who fail to respond to lithium.

In advocating the clinical use of carbamazepine, Post and Uhde (28) stressed that even though carbamazepine is not approved by the FDA for treatment of affective disorders, FDA regulations permit use of an approved drug for unlabeled indications when data clearly support this approach as a sound treatment (29). Post and Uhde argued that available data clearly support this option for carbamazepine. Jefferson et al. (30) adopted a more cautious approach, pointing out that use of carbamazepine in patients with affective disorders is still experimental and that further research is needed to identify its range of clinical effects and the risks associated with its long-term use.

In gauging the effectiveness of carbamazepine as a

preventive treatment for bipolar disorder, it is important to carefully examine the four randomized double-blind controlled trials that have evaluated carbamazepine in this capacity.

Watkins et al. (31) compared the relative efficacy of carbamazepine and lithium in maintaining remission after control of an acute episode of mania or major depression. Thirty-seven patients with bipolar disorder or major depressive disorder participated in the study; the proportion with bipolar disorder was not specified. For each patient, the investigators compared the time in recovery during study treatment with the time in recovery after a prior episode that had not been treated with maintenance medication. The investigators reported that both lithium and carbamazepine increased the time in remission but that lithium was "significantly the better drug." The average time in remission was 16 months with lithium and 9.4 months with carbamazepine. The percentage of patients who had a recurrence was not specified. A major difficulty in interpreting results from this trial is that, for ethical reasons, patients were given the option of taking antidepressant drugs temporarily if they perceived early symptoms of relapse. The option was taken by approximately 60% of the patients in each group. The use of an antidepressant was not interpreted as a sign of poor response to carbamazepine or lithium. There were no separate analyses for patients who received antidepressants nor any discussion of how this variable may have affected study outcome.

Placidi et al. (32) compared carbamazepine and lithium in the acute and prophylactic treatment of 83 patients with major affective, schizoaffective, or schizophreniform psychosis. During acute treatment, the dropout rate for patients with schizophrenic features was 50% for lithium and 20% for carbamazepine. With classical bipolar patients, there were fewer dropouts in the lithium group (20%) than in the carbamazepine group (35%). During the 2- to 36-month maintenance phase, the two treatment groups had equivalent recurrence rates. There were 12 recurrences in eight of 29 patients in the carbamazepine-treated group and nine recurrences in seven of 27 patients receiving lithium. Four patients in the carbamazepine group and one in the lithium group were dropped from the study because of adverse reactions. Inexplicably, there was no breakdown of results by diagnostic group for the maintenance phase, i.e., classical bipolar versus schizoaffective or schizophreniform, nor was there discussion of the possible effects of cotreatment with other drugs (neuroleptics, tricyclics, and benzodiazepines). Also, the study was somewhat atypical in that only two of the 83 patients entering the acute phase and none of the 56 patients entering the maintenance phase were men.

Lusznat et al. (33) compared carbamazepine and lithium in a two-phase study. Of 54 patients with a diagnosis of mania or hypomania who entered the 6-week "acute" phase, seven of the 27 patients in each treatment group failed to complete the first 6 weeks.

An additional 11 patients in the carbamazepine group and 15 in the lithium group were withdrawn from the study during the 12-month "follow-up" phase. Overall, only nine of the original 27 carbamazepine-treated patients and five of the 27 lithium-treated patients were classified as "satisfactory responders" by study criteria. The investigators suggested that insufficient dose may have contributed to the poor results in both treatment groups. One difficulty in interpreting results is that during the acute trial nearly all of the patients received a neuroleptic in addition to their study treatment. During the follow-up period, patients could be given antidepressants or neuroleptics when clinically indicated. Only five carbamazepine-treated patients were able to complete the follow-up period without receiving additional medication.

Okuma et al. (34) conducted the only study to compare carbamazepine to a placebo. This was an eight-center collaborative study that treated a total of 10 patients with carbamazepine and nine patients with placebo. Outcome was evaluated with a global rating scale of prophylactic efficacy developed by the collaborators. The investigators report that six of the 10 carbamazepine-treated patients and two of the nine patients receiving placebo showed a marked or moderate response; the difference between groups failed to reach statistical significance at the $p=0.05$ level. It was concluded that carbamazepine has a "tendency to prevent the recurrence of manic and depressive episodes."

In summary, the four double-blind controlled studies suggested that carbamazepine may be a promising preventive treatment for bipolar disorder, but they do not constitute the substantial demonstration of efficacy that is required for FDA approval. The studies collectively evaluated carbamazepine in fewer than 50 bipolar patients. In two of the studies (31, 32), results are not presented separately for bipolar patients and other diagnostic groups, and in one study (31), the patients were permitted the option of using antidepressant medication at any time during the trial.

The strongest evidence for the prophylactic efficacy of carbamazepine comes from other design paradigms: 1) mirror-image longitudinal trials in which the course of illness during treatment is compared to the course of illness during an equivalent time preceding the treatment (35), 2) longitudinal trials in which the test drug is periodically discontinued and/or replaced by a placebo (36, 37), and 3) long-term open trials evaluating the test drug in patients who have failed to respond to traditional treatments or have a recent history of frequent recurrences (38-41).

Results with the drug were positive in most of the trials in which these designs were used. However, many of the patients had carbamazepine added to a previously ineffective treatment regimen, usually lithium. Thus, the preventive efficacy of carbamazepine alone remains at issue. There is evidence suggesting a subgroup that may benefit more from the combination of lithium and carbamazepine than from either treatment alone (12, 33, 41-44), but this finding has not

been subjected to a rigorous controlled study. Also unresolved is the issue of whether or not carbamazepine should be used only with patients who are resistant to or cannot tolerate lithium. Some clinicians now recommend that certain subgroups of patients, such as those with rapid cycles, be treated initially with carbamazepine, either as a single agent or in combination with lithium (28). It would not be surprising if carbamazepine becomes a treatment of first choice with these patients.

Clearly, more information is required on the appropriate use of carbamazepine in bipolar disorder. Before clinicians are encouraged to view carbamazepine as an established long-term treatment for bipolar patients, carefully designed, prospective, controlled studies with adequate sample sizes are needed to confirm the efficacy and safety of carbamazepine and to establish its specific indications and range of clinical effects. Of particular importance is the establishment of accepted guidelines for hematologic monitoring for the rare but potentially lethal side effects of agranulocytosis or aplastic anemia (45).

Valproic acid. The positive reports for carbamazepine in bipolar illness spurred interest in two other anticonvulsants, valproic acid and clonazepam, as possible treatments for bipolar patients. Of the two, valproic acid has received the most attention as a long-term preventive treatment. Several open clinical trials evaluating the combination of valproic acid and lithium or valproic acid alone reported moderate to good prophylactic response (46–51). However, there has been no direct comparison of valproic acid with lithium, carbamazepine, or other treatments for bipolar disorder. A few case reports have suggested that some patients who do not respond to lithium or carbamazepine may be responsive to the combination of valproic acid and lithium (28), but this requires confirmation in systematic trials.

Few side effects have been reported in psychiatric patients receiving valproic acid. However, there are several reports of fatal hepatotoxicity in patients receiving valproic acid for seizure disorders. Although these hepatic failures have been confined largely to children under 10 years of age who were taking other anticonvulsants in addition to valproic acid (52), they are still a legitimate concern with long-term treatment of bipolar disorder, and periodic liver function tests are recommended (53).

Clonazepam. Clonazepam, a potent benzodiazepine derivative that has been used primarily as an anticonvulsant, has shown some value as an adjunctive treatment for acute mania (54–57). It is unclear whether the drug's effects are due to nonspecific sedation or to specific antimanic properties.

Clonazepam has been evaluated as a preventive maintenance treatment in only a few patients (58), and the results have been relatively negative. When it is given for seizure disorders, tolerance and tachyphylaxis can develop after long-term use (59). In addition, the potential for addiction and withdrawal reactions

secondary to clonazepam could create serious problems in a population notorious for noncompliance and abrupt discontinuation of medication (60). Thus, clonazepam does not appear to be a viable option for long-term continuous treatment, although it may provide some benefit as an adjunctive or substitute treatment for neuroleptics during early stages of a manic recurrence. In particular, the addition of clonazepam may allow a decrease in neuroleptic dose.

Calcium Channel Blockers

Calcium channel blockers are used primarily to treat supraventricular arrhythmias, anginas, and hypertension. Their principal action is to block calcium influx into cells. They share several pharmacologic properties with lithium and, in recent years, have attracted interest as a potential treatment for mania. Most of the interest has centered on verapamil, the oldest of the calcium blockers.

Several reports on the use of verapamil in treating acute mania suggest that the drug has antimanic properties (61–65). However, a recent study of verapamil therapy in eight patients with lithium-resistant mania or hypomania reported that none of the patients showed improvement (66). Verapamil should be used cautiously with carbamazepine or lithium. The drug can increase the risk of carbamazepine neurotoxicity (67) and may lower serum lithium level by increasing lithium excretion (68). Evaluation of verapamil as a long-term maintenance treatment has been based on a four-patient sample (66) and a few case reports and is too limited to draw any conclusions. Preliminary data suggest that verapamil may be useful in preventing pharmacologically induced mania and hypomania (66, 69, 70).

There are isolated reports on the antimanic effects of other calcium antagonists, such as diltiazem (71) and nifedipine (72), but none involving long-term maintenance treatment.

Antidepressants

Two multihospital collaborative studies (8, 73) found the tricyclic antidepressant imipramine to be significantly less effective than lithium in preventing manic episodes and equally as effective in preventing depressive episodes. In both studies, over 50% of the imipramine-treated patients developed a manic episode. One of the studies compared imipramine with placebo and reported no significant difference in incidence of recurrences between the two treatments (8).

The only other antidepressant to be evaluated in a long-term maintenance study in bipolar disorder is bupropion, a unicyclic compound with an unclear biochemical mode of action. Bupropion was approved by the FDA in late 1985 for patients who were refractory to or intolerant of other antidepressant medications but was voluntarily withdrawn from the market a few months later for further evaluation of the drug's sei-

zure potential in the general population (74). Some clinicians regard bupropion as a promising alternative to lithium because of its purported effectiveness in protecting against manic recurrences (75). Results from four studies (75–78), including one small-sample comparison of the drug with placebo (77), suggest that bupropion merits further evaluation as a long-term maintenance treatment in patients who fail to respond to or tolerate lithium. There has been no comparison of bupropion with lithium and only limited published data on the combination of lithium and bupropion. Further exploration of bupropion's effectiveness must await results from an ongoing multicenter study designed to determine the incidence of seizures with the drug.

In the 1970s, the combination of lithium and a tricyclic antidepressant was regarded as the most promising of the potential long-term maintenance treatments of bipolar disorder. The rationale for the combination was that lithium would protect the patient against manic recurrences and that the tricyclic would protect against depressive recurrences. One multicenter study (79) reported that the combination of lithium and imipramine provided no advantage over lithium alone. A second multicenter trial (73) indicated that the combination of lithium and imipramine was no more effective than lithium alone in preventing a recurrence after recovery from an acute episode, but it has been recently reported that this combination may lengthen the period between recovery and recurrence by several months (80).

Antipsychotic Drugs

The neuroleptic drugs are often used in the initial stages of acute mania to provide rapid control of psychopathology, particularly with very hyperactive or disturbed psychotic patients. Antipsychotic drugs produce a more rapid response than lithium, which may require up to 10 days for a therapeutic effect (81). Lithium may be administered concomitantly or added to the antipsychotic regimen after the initial therapeutic response. Because of the risk of tardive dyskinesia, the antipsychotic drug is often tapered and discontinued to allow continuation of lithium alone for maintenance treatment. Patients taking antipsychotic drugs in conjunction with lithium should be monitored for symptoms of neurotoxicity or neuroleptic malignant syndrome. Both conditions are rare but can result in death or permanent neurotoxic damage (82, 83).

Antipsychotic drugs are not recommended for long-term use in bipolar disorder. However, patients who suffer repeated manic recurrences while receiving lithium sometimes are treated with a neuroleptic alone or in combination with lithium. In such cases, the risk of tardive dyskinesia and other adverse effects of antipsychotic drug treatment is regarded as less of a danger than the highly disruptive and life-threatening consequences of repeated manic attacks. Evidence suggesting that patients with major affective disorders are at

higher risk for tardive dyskinesia than patients with schizophrenia makes decisions about using an antipsychotic drug all the more difficult (84). There is need for clearer definition of patients for whom this option is justifiable.

The only antipsychotic drug to be evaluated as a long-term treatment in bipolar disorder is a depot preparation, flupenthixol decanoate, and the results have been generally unfavorable. A multicenter study (85) comparing flupenthixol and lithium found no difference in the incidence of recurrences between the two groups; however, neither group showed significant improvement over the prestudy course of illness. The lack of effect with lithium was attributed to a "prognostically negative" selection of patients. A recent study comparing flupenthixol to an injected placebo failed to demonstrate greater efficacy with the drug (86). Flupenthixol is not available in the United States.

Treatment of Lithium-Resistant Rapid Cyclers

Patients with rapid-cycling bipolar disorder who have failed to respond to lithium have been the focus of a number of maintenance trials. There are several reports of positive findings, mainly from small-sample open trials. These results are preliminary and require further investigation.

Treatments reported to be effective in stabilizing the course of rapid-cycling bipolar disorder include carbamazepine alone or in combination with lithium (40, 41, 87), such thyroid medications as L-thyroxine and liothyronine (88, 89), haloperidol decanoate (90), the combination of the type A monoamine oxidase inhibitor clorgyline and lithium (91), valproic acid (48), verapamil (92), and repetitive sleep deprivation (93). Investigators have also focused on the role of antidepressants in rapid-cycling disorders. Some investigators suggest that the use of antidepressants to treat depressions occurring during lithium maintenance may accentuate rapid cycling and that withdrawing the antidepressant may be the most effective treatment (13, 92, 94). Kupopulos et al. (95) recommended the avoidance of an antidepressant with patients who have a history of developing hypomania after the depressive episode. Their rationale was that use of an antidepressant intensifies the postdepressive hypomania and makes it refractory to lithium. This strategy has not been studied in prospective trials. Without strong supportive data, there may be ethical concerns about allowing patients to endure a severe depressive episode without antidepressant treatment. Milder, tolerable depressive episodes in patients taking only lithium may afford a better opportunity to evaluate the strategy.

APPROPRIATE USE OF LITHIUM THERAPY

Often the best therapeutic approach with patients who appear to be refractory to lithium and in need of an alternative treatment is a reassessment of the lith-

ium regimen and a search for nonpharmacologic factors, such as psychosocial stresses, that may be contributing to the poor response. Before assuming that lithium is ineffective, the clinician should determine if the patient has an adequate serum lithium level and is adhering to the medication schedule. Although some patients may respond with serum levels as low as 0.5 to 0.6 meq/liter (96, 97), others may require levels as high as 0.8 to 1.2 meq/liter (98, 99). Recurrences that occur at a low serum level in patients who can tolerate higher doses should cause one to question the adequacy of dose.

An often neglected contributor to nonresponse is the patient's nonadherence to the medication schedule. Surveys indicate that 25%–50% of patients receiving long-term maintenance drug therapy discontinue medication, reduce dose, or otherwise fail to take medication as prescribed (100, 101). Many suffer recurrences as a result. A study of patients who discontinued lithium against medical advice at two major affective disorder clinics (100) found that side effects, especially memory problems, polyuria, weight gain, and tremor, were the most frequently cited reasons for noncompliance. Other reasons were disturbance at having a chronic illness (symbolized by the necessity of indefinite lithium therapy), loss of creativity, feeling well and seeing no need to continue medication, and reduced productivity. Among the reported strategies for improving adherence to treatment programs are 1) minimizing annoying side effects, 2) psychoeducational programs aimed at educating the patient and family about the disorder, its treatment, adverse reactions, and the consequences of prematurely stopping medication (102, 103), and 3) group sessions to discuss lithium treatment and concerns with the illness (104, 105). Individual and group psychotherapy may also lead to improved compliance in taking medication and better recognition of early signs of an emerging episode (100, 106).

The possibility of lithium-induced hypothyroidism should be considered for patients who develop depression during lithium treatment, especially if the depression is characterized by apathy, fatigue, psychomotor retardation, and other hypothyroid-like symptoms. Rapid cycling, in particular, may be associated with hypothyroidism and warrants an evaluation of thyroid status and supplemental thyroid if indicated.

SUMMARY

The search for alternatives to lithium therapy for the preventive treatment of bipolar disorder has provided promising leads that require further investigation. However, the carefully designed, prospective, double-blind studies that are needed to provide substantial evidence of drug efficacy have not been conducted. Carbamazepine, the most extensively studied of the alternatives to lithium, still awaits a well-designed controlled study with adequate statistical power to estab-

lish its efficacy for preventive treatment. The published controlled trials for carbamazepine are either small in sample size or flawed in design.

There are still critical unresolved issues regarding carbamazepine therapy that have not been adequately addressed in the reported therapeutic trials. For example, there is a need to establish how carbamazepine alone compares to the combination of carbamazepine and lithium and to lithium alone during preventive treatment. Another unresolved issue is whether carbamazepine alone or in combination with lithium is an appropriate first line prophylactic treatment for certain subgroups of patients (e.g., rapid cyclers) or should be limited to patients who are resistant to or unable to tolerate lithium.

The other potential alternatives to lithium maintenance treatment discussed in this review are less well-studied than carbamazepine. Valproic acid and bupropion (if and when it reenters the market) appear to be the most logical candidates for further evaluation. The circumstances under which antidepressant and antipsychotic drugs should be used during long-term treatment also need to be clarified in carefully designed trials.

The need for definitive, controlled, preventive maintenance trials does not disparage preliminary open label trials and exploratory controlled studies of promising agents. These trials provide the framework and justification for the expensive and time-consuming, large-sample controlled studies that are necessary to confirm the drug's efficacy and more sharply define its clinical indications. However, until these confirmatory studies are conducted, aggressive clinical utilization of the alternative treatments should be tempered by the limitations of the available research data.

While research continues, there is the practical problem of how to treat patients who are refractory and/or intolerant to lithium. These patients obviously cannot wait for the development of new treatment options or more definitive evaluation of existing treatments. Despite the need for more systematic study, carbamazepine is the best evaluated and most well-documented alternative to lithium and is the logical next choice when lithium therapy is inadequate. Carbamazepine may be added to the lithium regimen (with appropriate reduction in the lithium dose) or used as a single agent. Valproic acid is also mentioned as a promising alternative to lithium; however, relatively few data have been collected on its use as a preventive treatment, and it is not high on most of the published decision trees for preventive therapy of bipolar disorder. Antipsychotic drugs alone or in combination with lithium remain an option for patients who suffer repeated manic episodes while receiving lithium; however, the benefits of antipsychotic treatment must be carefully weighed against the risk of tardive dyskinesia and other adverse reactions. Carbamazepine does not appear to produce tardive dyskinesia and may be a safer alternative for long-term treatment. Adjunctive antidepressant therapy may be a useful alternative for preventing depres-

sive episodes in some patients who fail to respond to lithium, but the risk of inducing manic or hypomanic attacks must be considered. Finally, one of the most productive strategies in the face of a poor lithium response is to reassess the lithium regimen for adequacy of dose, examine patient compliance in taking medication, and search for nonpharmacologic contributory factors. These safeguards may avoid similar problems with any replacement treatment for lithium.

REFERENCES

1. Medical Practice Project: A State-of-the-Science Report for the Office of the Assistant Secretary for the US Department of Health, Education and Welfare. Baltimore, Policy Research, 1979
2. Robins LN, Helzer JE, Weissman MM, et al: Lifetime prevalence of psychiatric disorders in three sites. *Arch Gen Psychiatry* 1984; 41:949-958
3. Winokur G, Clayton PJ, Reich T: Manic Depressive Disease. St Louis, CV Mosby, 1969
4. Baastrup PC, Poulson JC, Schou M, et al: Prophylactic lithium: double-blind discontinuation in manic-depressive and recurrent disorders. *Lancet* 1970; 2:326-330
5. Coppen A, Noguera R, Baily J, et al: Prophylactic lithium in affective disorders. *Lancet* 1971; 2:275-279
6. Cundall RL, Brooks PW, Murray LG: Controlled evaluation of lithium prophylaxis in affective disorders. *Psychol Med* 1972; 3:308-311
7. Prien RF, Caffey EM, Klett CF: Prophylactic efficacy of lithium carbonate in manic-depressive illness. *Arch Gen Psychiatry* 1973; 28:337-341
8. Prien RF, Klett CF, Caffey EM: Lithium carbonate and imipramine in prevention of affective episodes. *Arch Gen Psychiatry* 1973; 29:420-425
9. Fieve RR, Kumbaraci T, Dunner DL: Lithium prophylaxis of depression in bipolar I, bipolar II, and unipolar patients. *Am J Psychiatry* 1976; 133:925-929
10. Schou M: Lithium Treatment of Manic-Depressive Illness: A Practical Guide. Basel, S Karger, 1980
11. Dunner DL, Patrick V, Fieve RR: Rapid cycling manic-depressive patients. *Compr Psychiatry* 1977; 18:561-566
12. Post RM, Uhde TW: Refractory manias and alternatives to lithium treatment, in *Depression and Mania*. Edited by Georgotas A, Cancro R. New York, Elsevier, 1988
13. Reginadi D, Tondo L, Floris G, et al: Poor prophylactic lithium response due to antidepressants. *Int Pharmacopsychiatry* 1981; 16:124-128
14. Himmelhoch JM, Garfinkel ME: Sources of lithium resistance in mixed mania. *Psychopharmacol Bull* 1986; 22:613-620
15. Prien RF, Himmelhoch JM, Kupfer DJ: Treatment of mixed mania. *J Affective Disord* 1988; 15:9-15
16. Secunda SK, Katz MM, Swann A, et al: Mixed mania: diagnosis and treatment, in *Mania: New Research and Treatment*. Edited by Swann A. Washington, DC, American Psychiatric Press, 1986
17. Johnson FN: Predicting lithium responders and nonresponders: psychological indicators, in *Handbook of Lithium Therapy*. Edited by Johnson FN. Lancaster, England, MTP Press, 1980
18. Maj M, Arena F, Lovero N, et al: Factors associated with response to lithium prophylaxis in DSM-III major depression and bipolar disorder. *Pharmacopsychiatry* 1985; 18:309-313
19. Weinstein MR: Lithium treatment of women during pregnancy and in the post-delivery period, in *Handbook of Lithium Therapy*. Edited by Johnson FN. Lancaster, England, MTP Press, 1980
20. Prien R: Long-term prophylactic pharmacologic treatment of bipolar illness, in *Psychiatry Update: The American Psychiatric Association Annual Review*, vol. 2. Edited by Grinspoon L. Washington, DC, American Psychiatric Press, 1983
21. Ayd FJ: Psychopharmacology update: alternatives for lithium. *Psychiatr Annals* 1984; 7:30-32
22. Lerer B: Alternative therapies for bipolar disorder. *J Clin Psychiatry* 1985; 46:309-315
23. NIMH/NIH Consensus Development Conference: mood disorders: pharmacologic prevention of recurrences. *Am J Psychiatry* 1985; 142:469-476
24. Okuma T, Kishimoto A, Inoue K, et al: Antimanic and prophylactic effects of carbamazepine on manic-depressive psychosis. *Folia Psychiatr Neurol Jpn* 1973; 27:283-297
25. Takezaki H, Hanaoka M: The use of carbamazepine (Tegretol) in the control of manic-depressive psychosis and other manic-depressive states. *Clin Psychiatry* 1971; 13:173-183
26. Dalby MA: Behavioral effects of carbamazepine, in *Complex Partial Seizures and Their Treatment: Advances in Neurology*, vol II. Edited by Penry JK, Daly DD. New York, Raven Press, 1975
27. Post RM, Uhde TW, Rubinow DR, et al: Antimanic effects of carbamazepine: mechanism of action and implications for the biochemistry of manic-depressive illness, in *Mania: New Research and Treatment*. Edited by Swann A. Washington, DC, American Psychiatric Press, 1986
28. Post RM, Uhde TW: Clinical approaches to treatment-resistant bipolar illness, in *Psychiatry Update: American Psychiatric Association Annual Review*, vol. 6. Edited by Hales RE, Frances AJ. Washington, DC, American Psychiatric Press, 1987
29. Food and Drug Administration: Use of approved drugs for unlabeled indications. *FDA Drug Bull* 1982; 12:4-5
30. Jefferson JW, Greist JH, Ackerman DL, et al: *Lithium Encyclopedia for Clinical Practice*, 2nd ed. Washington, DC, American Psychiatric Press, 1987
31. Watkins SE, Callender K, Thomas DR, et al: The effect of carbamazepine and lithium on remission from affective illness. *Br J Psychiatry* 1987; 150:180-182
32. Placidi GF, Lenzi A, Lazzarini F, et al: The comparative efficacy and safety of carbamazepine versus lithium: a randomized, double-blind 3-year trial in 83 patients. *J Clin Psychiatry* 1986; 47:490-494
33. Luszkat RM, Murphy DP, Nunn CMH: Carbamazepine vs lithium in the treatment and prophylaxis of mania. *Br J Psychiatry* 1988; 153:198-204
34. Okuma T, Inanaga K, Otsuki S, et al: A preliminary double-blind study of the efficacy of carbamazepine in prophylaxis of manic-depressive illness. *Psychopharmacology* 1981; 73:95-96
35. Shukla S, Cook BL, Miller MG: Lithium-carbamazepine versus lithium-neuroleptic prophylaxis in bipolar illness. *J Affective Disord* 1985; 9:219-222
36. Ballinger JC, Post RM: Carbamazepine in manic-depressive illness: a new treatment. *Am J Psychiatry* 1980; 137:782-790
37. Post RM, Uhde TW, Ballinger JC, et al: Prophylactic efficacy of carbamazepine in manic-depressive illness. *Am J Psychiatry* 1983; 140:1602-1604
38. Fawcett J, Kravitz HM: The long-term maintenance of bipolar disorders with lithium, carbamazepine, and antidepressants. *J Clin Psychiatry* 1985; 46:58-60
39. Gaspar M, Kielholz P: Carbamazepine treatment in therapy-resistant patients with manic-depressive psychosis, in *Preliminary Results With Anticonvulsants in Affective Disorders*. Edited by Emrich HM, Okuma T, Muller AA. Amsterdam, Elsevier, 1984
40. Kishimoto A, Ogura C, Hazama H, et al: Long-term prophylactic effects of carbamazepine in affective disorder. *Br J Psychiatry* 1983; 143:327-331
41. Stromgen LS, Boller S: Carbamazepine in treatment and prophylaxis of manic-depressive disorder. *Psychiatr Dev* 1985; 4:349-367
42. Lipinski JF, Pope HG Jr: Possible synergistic action between carbamazepine and lithium carbonate in the treatment of three acutely manic patients. *Am J Psychiatry* 1982; 139:948-949

43. Moss GR, James CR: Carbamazepine and lithium carbonate synergism in mania. *Arch Gen Psychiatry* 1983; 40:588-589
44. Omura F, Kishimoto A, Tsutsui T, et al: Combined therapy of lithium and carbamazepine in bipolar affective disorders. *Folia Psychiatr Neurol Jpn* 1984; 38:401-402
45. Balon R, Berchou R: Hematologic side effects of psychotropic drugs. *Psychosomatics* 1986; 27:119-120
46. Brennan MJW, Sandyk R, Borsook D: Use of sodium-valproate in the management of affective disorders: basic and clinical aspects, in *Anticonvulsants in Affective Disorders*. Edited by Emrich HM, Okuma T, Muller AA. Amsterdam, Excerpta Medica, 1984
47. Emrich HM, Dose M, von Zerssen D: The use of sodium-valproate and of oxycarbazepine in patients with affective disorders. *J Affective Disord* 1985; 8:243-250
48. McElroy SL, Keck PE, Pope HG, et al: Valproate in the treatment of rapid cycling bipolar disorder. *J Clin Psychopharmacol* 1988; 8:275-279
49. Puzynski S, Klosiewicz L: Valproic acid amide in the treatment of affective and schizoaffective disorders. *J Affective Disord* 1984; 6:115-121
50. Svestka J, Nahunek K, Ceskova E: [Sodium valproate in the prophylaxis of manic-depressive psychosis.] *Acta Nervenhelk (Suppl)* 1987; 29:187-188 (Czech)
51. Vencovsky E, Soucek K, Kabes J: Prophylactic effect of dipropylacetamide in patients with bipolar affective disorder—short communication, in *Anticonvulsants in Affective Disorders*. Edited by Emrich HM, Okuma T, Muller AA. Amsterdam, Excerpta Medica, 1984
52. Dreifuss FE, Santilli RN, Langer DH, et al: Valproic acid hepatic fatalities: a retrospective review. *Neurology* 1987; 37:379-385
53. Schatzberg AF, Cole JO: *Manual of Clinical Psychopharmacology*. American Psychiatric Press, 1986
54. Chouinard G: Antimanic effects of clonazepam. *Biol Psychiatry* 1983; 18:451-466
55. Chouinard G: Clonazepam in acute and maintenance treatment of bipolar affective disorder. *J Clin Psychiatry* 1987; 48 (Oct suppl):29-36
56. Freinhar JP, Alvarez WH: Use of clonazepam in two cases of acute mania. *J Clin Psychiatry* 1985; 46:29-30
57. Victor BS, Link NA, Binder RL, et al: Use of clonazepam in mania and schizoaffective disorders. *Am J Psychiatry* 1984; 141:1111-1112
58. Aronson TA, Shulka S, Hirschowitz J: Clonazepam treatment of five lithium-refractory patients with bipolar disorder. *Am J Psychiatry* 1989; 146:77-80
59. Browne TR: Drug therapy: clonazepam. *N Engl J Med* 1978; 299:812-816
60. Colwell BL, Lopez JR: Clonazepam in mania. *Drug Intell Clin Pharm* 1987; 21:794-795
61. Brotman AW, Farhadi AM, Gelenberg AJ: Verapamil treatment of acute mania. *J Clin Psychiatry* 1986; 47:136-138
62. Dubovsky SL, Franks RD: Intracellular calcium ions in affective disorders: a review and a hypothesis. *Biol Psychiatry* 1983; 18:781-797
63. Dubovsky SL, Franks RD, Murphy J: Calcium antagonists in mania: a double-blind study of verapamil. *Psychiatry Res* 1986; 18:309-320
64. Giannini AJ, Houser WL Jr, Loiselle RH, et al: Antimanic effects of verapamil. *Am J Psychiatry* 1984; 141:1602-1603
65. Solomon L, Williamson P: Verapamil in bipolar illness. *Can J Psychiatry* 1986; 31:442-444
66. Barton BM, Gitlin MJ: Verapamil in treatment-resistant mania: an open trial. *J Clin Psychopharmacol* 1987; 7:101-103
67. MacPhee GJ, McInnes GT, Thompson GG, et al: Verapamil potentiates carbamazepine neurotoxicity: a clinically important inhibitory interaction. *Lancet* 1986; 1:700-703
68. Weinrauch LA, Belok S, D'Elia JA: Decreased serum lithium during verapamil therapy. *Am Heart J* 1984; 108:1378-1380
69. Dubovsky SL, Franks RD, Schrier D: Phenelzine-induced hypomania: effect of verapamil. *Biol Psychiatry* 1985; 20:1009-1014
70. Gitlin MJ, Weiss J: Verapamil as maintenance treatment in bipolar illness: a case report. *J Clin Psychopharmacol* 1984; 4:341-343
71. Caillard V: Treatment of mania using a calcium antagonist: preliminary trial. *Neuropsychobiology* 1985; 14:23-26
72. Goldstein JA: Calcium and neurotransmission (letter). *Biol Psychiatry* 1984; 19:465-466
73. Prien RF, Kupfer DJ, Mansky PA, et al: Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. *Arch Gen Psychiatry* 1984; 41:1096-1104
74. Wellbutrin study. *Psychiatry Drug Alerts* 1987; 1:67
75. Wright G, Galloway L, Kim J, et al: Bupropion in the long-term treatment of cyclic mood disorders: mood stabilizing effects. *J Clin Psychiatry* 1985; 46:22-25
76. Gardner EA: Long-term preventive care in depression: the use of bupropion in patients intolerant of other antidepressants. *J Clin Psychiatry* 1983; 44 (5, section 2):157-162
77. Othmer E, Othmer SC, Desouza C: New treatment for lithium problem bipolar patients, in *New Research Abstracts, 138th Annual Meeting of the American Psychiatric Association*. Washington, DC, APA, 1985
78. Shopsin B: Bupropion's prophylactic efficacy in bipolar affective illness. *J Clin Psychiatry* 1983; 44:163-169
79. Quitkin FM, Kane J, Rifkin A, et al: Prophylactic lithium carbonate with and without imipramine for bipolar I patients. *Arch Gen Psychiatry* 1981; 38:902-907
80. Shapiro D, Quitkin F, Fleiss J: Type of index episode and response to maintenance drug therapy in bipolar illness. *Arch Gen Psychiatry* (in press)
81. Prien RF, Caffey EM, Klett CJ: A comparison of lithium carbonate and chlorpromazine in the treatment of acute mania. *Arch Gen Psychiatry* 1972; 26:146-153
82. Amdisen A: Lithium and drug interactions. *Drugs* 1982; 24:133-139
83. Dunner DL, Clayton PJ: Drug treatment of bipolar disorder, in *Psychopharmacology: The Third Generation of Progress*. Edited by Meltzer HY. New York, Raven Press, 1987
84. Kane JM: The role of neuroleptics in manic-depressive illness. *J Clin Psychiatry* 1988; 49 (Nov suppl):12-14
85. Ahlfors UG, Baastrup PC, Dencker SJ, et al: Flupenthixol decanoate in recurrent manic-depressive illness: a comparison with lithium. *Acta Psychiatr Scand* 1981; 64:226-237
86. Esparon J, Kolloori J, Naylor GJ, et al: Comparison of the prophylactic action of flupenthixol with placebo in lithium-treated manic-depressive patients. *Br J Psychiatry* 1986; 148:723-725
87. Post RM, Uhde TW: Carbamazepine in bipolar illness. *Psychopharmacol Bull* 1985; 21:10-17
88. von Hoffman G, Bolen H: Therapeutic investigation of chronic manic depressive illness. *Arzneimittelforschung* 1969; 19:455-456
89. Stancer HC, Persad E: Treatment of intractable rapid-cycling manic-depressive disorder with levothyroxine. *Arch Gen Psychiatry* 1982; 39:311-312
90. Lowe MR: Treatment of rapid cycling affective illness (letter). *Br J Psychiatry* 1985; 146:558
91. Potter WZ, Murphy DL, Wehr TA, et al: Clorgyline: a new treatment for patients with refractory rapid-cycling disorder. *Arch Gen Psychiatry* 1982; 39:505-510
92. Wehr TA, Goodwin FK: Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry* 1979; 36:555-559
93. Roy-Byrne PP, Joffe RT, Uhde TW, et al: Approaches to the evaluation and treatment of rapid cycling affective illness. *Br J Psychiatry* 1984; 145:543-550
94. Wehr TA, Sack DA, Rosenthal NE, et al: Rapid cycling affective disorders and treatment response in 51 patients. *Am J Psychiatry* 1988; 145:179-183
95. Kupopulos A, Tondo L: Lithium nonresponders and their treatment, in *Handbook of Lithium Therapy*. Edited by Johnson FN. Lancaster, England, MTP Press, 1980
96. Foster JR, Rosenthal JS: Lithium therapy of the elderly. *Ibid*

97. Hullin RP: Minimum serum levels for effective prophylaxis. *Ibid*
98. Prien RF, Caffey EM Jr: Relationship between dosage and response to lithium prophylaxis in recurrent depression. *Am J Psychiatry* 1976; 133:567-570
99. Waters B, Lapierre YD, Gagnon A, et al: Determination of the optimal concentration of lithium for the prophylaxis of manic-depressive disorder. *Biol Psychiatry* 1982; 17:1323-1329
100. Jamison KR, Goodwin FK: Psychotherapeutic issues, in *Psychiatry Update: The American Psychiatric Association Annual Review*, vol. 2. Edited by Grinspoon L. Washington, DC, American Psychiatric Press, 1983
101. Van Putten T: Why do patients with manic-depressive illness stop their lithium? *Compr Psychiatry* 1975; 16:179-183
102. Frank E, Prien RF, Kupfer DJ, et al: Implications of noncompliance on research in affective disorders. *Psychopharmacol Bull* 1985; 21:37-42
103. Seltzer A, Roncari I, Garfinkel P: Effects of patient education on medication compliance. *Can J Psychiatry* 1980; 25:638-645
104. Rosen AM: Group management of lithium prophylaxis. *J Psychiatr Treatment and Evaluation* 1982; 4:181-183
105. Volkmar FR, Bacon S, Shakir SA, et al: Group therapy in the management of manic-depressive illness. *Am J Psychother* 1981; 35:226-234
106. Jamison KR, Gerner RH, Goodwin FK: Patient and physician attitudes toward lithium: relationship to compliance. *Arch Gen Psychiatry* 1979; 36:866-869

Neurological Impairment in Violent Schizophrenic Inpatients

Menahem I. Krakowski, M.D., Ph.D., Antonio Convit, M.D., Judith Jaeger, Ph.D.,
Shang Lin, Ph.D., and Jan Volavka, M.D., Ph.D.

This study relates violent behavior of schizophrenic inpatients to demographic, historical, EEG, neurological, and neuropsychological variables. Patients were classified into high (N=28), low (N=27), or no (N=34) violence groups. There were no significant differences among the groups on demographic or historical variables, except for prevalence of violent crime, which was higher in both violent groups than in nonviolent patients. Neurological and neuropsychological abnormalities differentiated the groups, with the high violence group evidencing more abnormalities than the other two groups in the area of integrative sensory and motor functions. The authors suggest that violence as well as neurological and neuropsychological deficits may characterize a more severe form of schizophrenia. (Am J Psychiatry 1989; 146:849-853)

Violence is frequently reported in schizophrenic inpatients (1-4). Diagnosis per se, however, yields minimal information as to the etiology of the violence. Variables of greater etiological significance reported to be associated with violence in general psychiatric populations include neurological impairment (5, 6), EEG abnormalities (5, 7), and a history of early environmental deprivation and physical abuse (6, 7). It has not been determined whether these variables are also associated with violence in schizophrenia.

Received April 4, 1988; revision received Dec. 7, 1988; accepted Feb. 2, 1989. From the Manhattan Psychiatric Center, New York, and the Nathan S. Kline Institute. Address reprint requests to Dr. Krakowski, Nathan S. Kline Institute, Orangeburg, NY 10962.

The authors thank the staff of the intensive psychiatric service for their cooperation in this study and Dr. Herman Weinreb and Dr. Bernard Wyszynski for their helpful suggestions.

Copyright © 1989 American Psychiatric Association.

It is important to differentiate conceptually between violent episodes (which can be rare occurrences in many patients) and the tendency toward violence (as evidenced by repeated episodes). It is the latter which is an enduring characteristic of patients and lends itself to an inquiry into predisposing traits. To our knowledge, this distinction has not been made in the psychiatric literature on violence. There is, in general, a failure to acknowledge the heterogeneity of violent behavior; patients have often been dichotomized simply into violent and nonviolent groups. Our study compares schizophrenic patients who showed high degrees of violence, low violence, and no violence on a variety of neurological, neuropsychological, demographic, historical, and EEG variables. We hypothesized that patients who are highly violent are more likely to have neurological deficits and a history of early environmental deprivation.

METHOD

Subjects

Subjects were inpatients selected from a 1,300-bed state psychiatric facility located in a large metropolitan area serving predominantly indigent, inner-city patients. Fifty-five schizophrenic patients consecutively admitted to a special unit designed for the management of violent behavior constituted the assaultive group. These patients had exhibited at least two instances of assaultive behavior on their home wards in the previous month; this behavior qualified them for transfer to the special unit. A group of 34 nonviolent schizophrenic patients selected from the same hospital constituted the control group. Control patients had been hospitalized for at least 6 months and had committed no serious acts of violence during the current

admission or during any prior admission to the hospital. The control group was selected so that its group distributions for age, sex, race, and chronicity of illness approximated as closely as possible the distributions of the group of violent patients.

Patients showed a varying degree of assaultiveness after transfer to the new ward and were further subdivided into "high violence" and "low violence" groups depending on the frequency of violent incidents after transfer. The 28 patients who had two or more incidents of verbal or physical assault or assault against property constituted the high violence group. The 27 patients who had one incident or none on the new ward made up the low violence group (all patients had been violent before transfer).

Procedure

Diagnosis of schizophrenia for all patients was established by consensus of two research psychiatrists who used *DSM-III* criteria; it was not based on chart diagnosis. The violent behaviors of interest in this study, as described in a previous paper (8), were physical assault (any physical aggressive act), verbal assault (a verbal threat of bodily harm) directed at another patient or a staff member, and assault against property. All patients underwent an extensive historical and demographic interview, a quantified neurological examination, and an EEG. Additional historical information was obtained from hospital records and family members whenever possible. A comprehensive neuropsychological examination was administered to a subgroup of violent patients, as described below. In addition to demographic variables, we noted patients' drug and alcohol use, self-reported suicide attempts, self-reported arrests and convictions for violent and non-violent crimes, and head trauma.

Family variables included parental substance abuse, parental psychiatric hospitalization, family intactness, and history of physical abuse as a child. A patient was considered to have been physically abused if the physical injury inflicted resulted in blood being drawn, welts being formed, or medical attention being required. The family intactness variable was a dichotomous variable that assesses whether or not the patient had lived in a stable home and had a steady relationship with his or her father or foster father up to the age of 15.

A quantified neurological scale (9) was administered by two physicians with formal training in neurology. In view of the risk of administering neurological examinations to violent patients, these physicians could not be blind to whether or not patients were violent; however, they were unaware of which patients would be in the high and low violence groups. Interrater reliability between two trained raters was measured with 32 patients. The intraclass correlation coefficient for the total neurological score in this sample was 0.91. The scale consisted of 56 items that included hard signs as well as soft signs. A score of 1 on any item

indicated abnormality, while 0 indicated normality. The neurological abnormality score for each patient consisted of the sum of the scores on all items administered divided by the number of items. Thus, the maximal abnormal total score was equal to 1.

All EEGs were recorded by using the International 10-20 system. They were recorded over 15 minutes, while patients were resting with eyes closed. No sleep EEGs were performed. All tracings were read by one of us (J.V.), who was blind to whether the patients were violent; the tracings were inspected for theta, delta, and sharp waves; discharges; lateralization; effect of hyperventilation; presence of low voltage; and normality.

A neuropsychologist (J.J.) administered a 4- to 6-hour comprehensive neuropsychological examination. It consisted of tests that were chosen as measures of the following four major functional systems: 1) verbal production and comprehension (verbal) (eight variables), 2) visual-spatial functions (visual) (nine variables), 3) attention, concentration, and memory (memory) (seven variables), and 4) motor sequencing and manual dexterity (manual dexterity) (three variables). The tests included the WAIS-R information (verbal), vocabulary (verbal), comprehension (verbal), similarities (verbal), arithmetic (memory), digit span (memory), picture completion (visual), picture arrangement (visual), block design (visual), object assembly (visual), and digit symbol (visual) tests; Boston Naming Test (verbal); Controlled Oral Word Association Test (verbal); Token Test (verbal); Peabody Individual Achievement Test-Reading Recognition and Reading Comprehension subtests (verbal); Finger Localization Test (visual); Benton Visual Retention Test (visual); Raven's Colored Progressive Matrices (visual); Purdue Pegboard (manual dexterity); competing motor programs test (manual dexterity); asymmetry of finger localization (manual dexterity); Sentence Repetition Test (memory); cancellation tests (time and errors) (memory); Multiple Choice Benton Visual Retention Test (memory); and temporal orientation (memory).

This battery was administered to 39 violent patients (22 in the high violence and 17 in the low violence groups) and 22 control patients. We attempted to test the entire study cohort but were unable to test 28 patients. Of these, five were too psychotic to cooperate with testing, one patient refused, and two were judged to be too violent, and 20 were not tested due to limitations in staff resources. The group distribution of untested patients reflected no biases: Six were in the high violent group, 10 in the low violent group, and 12 in the control group.

Data Analysis

The nonviolent control patients were compared to both the high violence and the low violence groups, and the two violent groups were compared to each other. Chi-square tests were used for categorical variables. For the continuous variables, analyses of variance (ANOVAs) were computed; when significant

they were followed by Duncan's multiple range tests to correct for multiple comparisons.

The neuropsychological data were analyzed globally by comparing the groups on the WAIS-R total IQ, verbal IQ, and performance IQ. In addition, the 27 neuropsychological variables (this number is obtained when WAIS-R subtests are treated separately) were compared. These variables were grouped a priori according to the predominant function being tested (no variable was included in more than one function). Patterns of results between functional groups were examined.

Logistic regression models (10) were used to simultaneously relate the violent group status (high versus control group, high versus low, and low versus control group) to multiple risk factors. These models were used to control for possible confounding variables, such as previous violent behavior, head trauma, and drug and alcohol abuse, by entering these variables in the equations.

RESULTS

There were no significant differences among the three groups for sex, race, age, or age at first hospitalization. There were 19 men and nine women in the high violence group, 23 men and four women in the low violence group, and 29 men and five women in the control group. The high violence group consisted of eight whites and 20 nonwhites; the low violence group, four whites and 23 nonwhites; and the control group, eight whites and 26 nonwhites. The mean \pm SD ages of the three groups were 29.2 ± 7.7 , 31.4 ± 7.1 , and 32.5 ± 8.5 years, respectively. The mean ages at first hospitalization were 17.1 ± 5.6 years, 18.1 ± 5.0 , and 19.6 ± 7.5 years, respectively. The fact that this was a state hospital population drawn from the inner city is reflected in the ethnic composition of our sample, which was predominantly nonwhite; this may limit the generalizability of our results. There were no significant differences among the three groups in alcohol or drug use, head trauma, suicide attempts, and arrest or conviction for nonviolent crimes. There were also no differences in parental substance abuse, parental psychiatric hospitalization, family intactness, and history of physical abuse as a child. However, significantly more of the patients in the high violence and low violence groups reported arrests for violent crimes than did the control group (39.3% [N=11] for high violence group versus 8.8% [N=3] for the control group, $\chi^2=8.67$, $df=1$, $p<0.01$; and 40.7% [N=11] for the low violence group versus 8.8% [N=3] for the control group, $\chi^2=8.1$, $df=1$, $p<0.01$). More high violence (32.1% [N=9]) and low violence (25.9% [N=7]) patients than control patients (5.9% [N=2]) reported convictions for violent crime; this difference was significant for both assaultive groups ($\chi^2=7.67$, $df=1$, $p<0.01$, and $\chi^2=4.52$, $df=1$, $p<0.05$, respectively).

There was a significant difference among the three groups in the neurological impairment score ($F=11.9$,

TABLE 1. Violent Schizophrenic Patients and Schizophrenic Control Subjects With Abnormal Neurological Signs

Abnormal Variable	Violent Patients ^a				Control Patients (N=34)	
	High Violence (N=28)		Low Violence (N=27)			
	N	%	N	%	N	%
Right-left orientation	11	39 ^{b,c}	4	15	7	21
Hopping	6	24 ^{d,e,f}	2	7	2	6
Hearing	9	32 ^{d,e}	4	15	1	3
Walking-associated movements	6	21 ^g	4	15	0	0
Arm drift	12	48 ^{f,g}	10	37	5	16 ^f
Pronation-supination	9	35 ^{c,e,f}	2	7	4	13 ^f
Finger-thumb opposition (left)	5	19 ^{d,e,f}	1	4	1	3
Tandem walk	9	33 ^{f,g,h}	1	4	1	3
Graphesthesia	11	39 ^{b,g}	4	15	3	9
Stereognosis	4	15 ^{b,f}	0	0	2	6

^aHigh violence patients committed two or more acts of verbal assault, physical assault, or destruction of property after transfer to special unit for management of violent behavior. Low violence patients committed one or no such acts.

^bSignificantly different from low violence group ($p<0.05$).

^cTrend toward significant difference from control group ($p<0.10$).

^dSignificantly different from control group ($p<0.05$).

^eTrend toward significant difference from low violence group ($p<0.10$).

^fPercent based on less than total sample.

^gSignificantly different from control group ($p<0.01$).

^hSignificantly different from low violence group ($p<0.01$).

$df=2$, 86, $p<0.001$, ANOVA). The mean \pm SD neurological impairment score of the high violence group (0.13 ± 0.10) was significantly higher than that of the low violence group (0.06 ± 0.06 ; $t=3.18$, $df=53$, $p<0.01$) and control group (0.05 ± 0.05 ; $t=4.01$, $df=59$, $p<0.01$, Duncan t tests for both comparisons). This difference remained significant after we accounted for the possible effects of medication by converting the doses of the various antipsychotic medications to chlorpromazine equivalents and used this variable as a covariate ($F=10.1$, $df=2$, 80, $p<0.001$, analysis of covariance). One hundred percent of the high violence, 82% (N=22) of the low violence, and 65% (N=22) of the nonviolent groups had one or more abnormalities on the neurological examination, while 89% (N=25), 74% (N=20), and 47% (N=16) of these groups, respectively, had two or more abnormalities.

To a certain extent, the significantly higher impairment score obtained by the high violence group on the neurological scale is due to the cumulative effect of multiple items. There were, however, a certain number of individual neurological signs that were found significantly more frequently in the high violence group than in the other two groups (table 1).

There were no significant differences among the three groups of patients in the frequency of EEGs read as abnormal, in presence of theta, delta, and sharp

TABLE 2. Scores of Schizophrenic Violent Patients and Schizophrenic Control Subjects on Visual-Spatial Function Tests

Test	Violent Patients ^a				Control Patients (N=22)	
	High Violence (N=22)		Low Violence (N=17)		Mean	SD
WAIS-R performance IQ	66.1 ^{b,c}	7.8	73.1	13.1	75.1	10.5
Picture completion	4.6 ^d	1.1	6.3	2.9	5.9	2.2
Picture arrangement	4.4 ^c	1.8	5.3	2.1	6.0	2.4
Block design	5.2 ^c	2.3	6.1	2.4	7.0	2.4
Object assembly	4.9	2.5	6.5	2.7	6.2	2.4
Digit symbol	3.5 ^c	1.7	4.4	1.7	4.8	1.9
Benton Visual Retention Test						
Correct answers	6.2 ^d	3.4	8.4	1.9	8.3	2.3
Errors	4.6 ^d	3.8	1.8	2.7	2.2	4.0
Finger Localization Test	54.2	4.2	54.9	4.7	53.5	6.5
Raven Colored Progressive Matrices IQ	69.1	20.3	78.7	15.0	81.7	17.4

^aHigh violence patients committed two or more acts of verbal assault, physical assault, or destruction of property after transfer to special unit for management of violent behavior. Low violence patients committed one or no such acts.

^bTrend toward significant difference from low violence group ($p \leq 0.10$; Duncan's *t* test was performed when ANOVA was significant).

^cSignificantly different from control group ($p \leq 0.05$).

^dSignificantly different from low violence and control groups ($p \leq 0.05$).

waves; discharges; lateralization; temporal focus; abnormal response to hyperventilation; or low voltage.

According to global neuropsychological test results, all three groups were impaired compared to the normative population. The mean \pm SD WAIS IQs for control (N=22), low violence (N=17), and high violence (N=22) groups were 75.0 ± 11.5 , 73.3 ± 15.4 , and 69.3 ± 9.6 , respectively. The mean \pm SD number of years of schooling completed by the control, low violence, and high violence groups were 10.4 ± 2.8 , 10.0 ± 2.6 , and 10.1 ± 2.5 , respectively. There were no significant differences in mean IQ or education level among the three groups.

A pattern of selective impairment in visual-spatial functions emerged among the high violence group, compared to both the low violence and control groups. This was reflected globally in the WAIS-R performance IQ, which included five of the nine visual-spatial tasks and differed significantly among the groups ($F=3.69$, $df=2$, 55 , $p \leq 0.05$, ANOVA). It was significantly lower in the high violence group than in the nonviolent control group, and there was a trend showing lower performance IQ in the high violence group than in the low violence group (see table 2). When we consider the various tests individually, there were six out of nine significant ANOVAs ($p \leq 0.05$) for the visual-spatial functions; none of the 18 variables from the three remaining functions was significant at this level. Dun-

can's multiple range tests revealed that the high violence and control groups differed the most. Comparison between low and high violence groups yielded a similar pattern, to a lesser degree. When control patients were compared to low violence patients, no statistically significant differences emerged (see table 2).

The logistic regression models were used to control for the possible confounding effects of drug and alcohol abuse, head trauma, and convictions for violent crimes. The effect of neurological impairment remained significant in differentiating high violent versus control and high violent versus low violent groups. Similarly, the effect of WAIS-R performance IQ and score on the Benton Visual Retention Test each remained significant in differentiating among these groups.

DISCUSSION

Both violent groups reported a higher rate of violent crime before hospitalization than did the nonviolent control group. Violence in these two groups of patients, then, was a recurrent phenomenon and was not restricted to the hospital environment.

The presence of neurological abnormalities was the factor that differentiated most clearly among the three groups, with the high violence group being most impaired and the nonviolent patients being least impaired. These differences could be delineated further, to a certain extent. On the neurological examination, the high violence group evidenced more prominently certain abnormalities such as impairments in stereognosis, graphesthesia, tandem walk, and walking-associated movements. On neuropsychological testing, this group demonstrated a selective impairment in visual-spatial functioning. The lack of significant difference between the groups on verbal functions, as well as on tasks involving attention and concentration, suggests that relative impairments on neurological variables and visual-spatial tasks were not caused by differences in the patients' ability to comprehend or attend to instructions on the neurological examination.

The fact that the three groups did not differ on the EEGs, or on many neuropsychological tests and some neurological items, points to discrete areas of functional impairment. The groups differed mostly in the area of integrative sensory function and complex coordination of motor activity.

What is the relationship between neurological impairment and violence? Neurological abnormalities could be the result of the violence. Violent patients are more often involved in fights that can result in head trauma and hence in neurological impairment. However, our results do not support such a hypothesis. Reports of head trauma were not different among the groups and did not affect the results. The neurological impairment, on the other hand, could be a cause of the violence. It might produce some disinhibitory effect which could result in poor control over violent impulses.

How could we account, then, for the higher prevalence

of neurological impairment in the violent schizophrenic patients? This finding may reflect an etiology unrelated to schizophrenia, such as drug or alcohol abuse. The groups, however, did not differ on these variables, nor did these factors contribute to the difference in neurological impairment. It is possible that the neurological deficits, above and beyond those found in the control group, may characterize a subgroup of patients with a more severe form of schizophrenia.

While the neurological signs present in schizophrenic patients have not been conclusively defined, there appear to be discrete areas of functional impairment, such as in integrative sensory and motor functions, as well as in the sequencing of motor patterns (11). More neurological signs have been found in more severe forms of the illness, such as schizophrenia with premorbid asocial behavior (12) and with a high number of relapses (13). These findings would be consistent with the neurological findings in our study, which are, for the most part, simply an exaggeration of those reported for schizophrenia. The higher prevalence of hearing impairment in the high violence group is not consistent with this hypothesis, but the hearing tests, which depend on the patient's report, may be influenced by various subjective factors other than primary sensory defect.

The discrete visual-spatial dysfunction on neuropsychological testing is consistent with such an integrative sensory and motor impairment. However, since visual-spatial tasks are usually thought to reflect right hemispheric functioning, our finding appears, on first consideration, to be inconsistent with another hypothesis, namely, that schizophrenia is associated with left hemispheric impairment (14). A critical review of the literature (15), however, suggests that dominant lobe dysfunction may characterize only milder and less chronic forms of schizophrenia in which thought disorder, rather than features of the chronic disease process (e.g., affective blunting, emotional withdrawal, and anhedonia), is the predominant symptom.

Tests of visual-spatial functions are more sensitive to dysfunction in integrative sensory function and complex motor coordination than are verbal tests. They are more likely than verbal tests to be timed, to involve processing of unique or new stimuli, and to reflect vulnerability to distraction. The verbal tests in this battery for the most part involved the assessment of previously learned material and its recollection. Schizophrenic patients have been shown to be slow in information processing, a finding that is more consistent in poor prognosis than good prognosis patients (16). Schizophrenic patients show greater distractibility and lower processing capacity on cognitive tasks than depressed patients and normal control subjects (17). Furthermore, it has been suggested that visual-spatial tasks, while selectively impaired in focal disease of the right hemisphere, may also be selectively affected in more globally distributed cerebral disease because of their dependence on response

time and the processing of new stimuli, rather than recall of familiar, previously learned material (18).

Thus, greater violence, as well as greater neurological and neuropsychological impairment, may be characteristic of a more severe form of schizophrenia. While it has often been assumed that more severe schizophrenia is characterized predominantly by negative symptoms, the presence of assaultive behavior would be consistent with certain reports in the literature (19) of prominent negative as well as positive symptoms in severely deteriorated schizophrenic patients.

REFERENCES

1. Shader RI, Jackson AH, Harmatz JS, et al: Patterns of violent behavior among schizophrenic inpatients. *Dis Nerv Syst* 1977; 38:13-16
2. Tardiff K, Sweillam A: Assault, suicide and mental illness. *Arch Gen Psychiatry* 1980; 37:164-169
3. Tardiff K, Sweillam A: Assaultive behavior among chronic inpatients. *Am J Psychiatry* 1982; 139:212-215
4. Craig TJ: An epidemiologic study of problems associated with violence among psychiatric inpatients. *Am J Psychiatry* 1982; 139:1262-1265
5. Lewis DO, Shanok SS, Pincus JH, et al: Violent juvenile delinquents: psychiatric, neurological, psychological and abuse factors. *J Am Acad Child Psychiatry* 1979; 18:307-319
6. Lewis DO, Shanok SS, Grant M, et al: Homicidally aggressive young children: neuropsychiatric and experiential correlates. *Am J Psychiatry* 1983; 140:148-153
7. Bach-y-Rita G, Lion JR, Climent CE, et al: Episodic dyscontrol: a study of 13C violent patients. *Am J Psychiatry* 1971; 127:1473-1478
8. Brizer DA, Convit A, Krakowski M, et al: A rating scale for reporting violence on psychiatric wards. *Hosp Community Psychiatry* 1987; 38:769-770
9. Convit A, Jaeger J, Lin S, et al: Prediction of violence in psychiatric inpatients, in *Biological Contributions to Crime Causation*. Edited by Moffitt TE, Mednick SA. Amsterdam, Martinus Nijhoff, 1988
10. Kleinbaum DG, Kupper LL, Morgenstern H: *Epidemiologic Research: Principles and Quantitative Methods*. New York, Van Nostrand Reinhold, 1982
11. Heinrichs DW, Buchanan RW: Significance and meaning of neurological signs in schizophrenia. *Am J Psychiatry* 1988; 145:11-18
12. Quitkin F, Rifkin A, Klein DF: Neurologic soft signs in schizophrenia and character disorders. *Arch Gen Psychiatry* 1976; 33:845-853
13. Tucker GJ, Campion EW, Silberfarb PM: Sensorimotor functions and cognitive disturbance in psychiatric patients. *Am J Psychiatry* 1975; 132:17-21
14. Flor-Henry P: *Cerebral Basis of Psychopathology*. Bristol, England, John Wright, 1983
15. Merrin EL: Schizophrenia and brain asymmetry: an evaluation of evidence for dominant lobe dysfunction. *J Nerv Ment Dis* 1981; 169:405-416
16. Saccuzzo DP, Braff DL: Early information processing deficit in schizophrenia: new findings using schizophrenic subgroups and manic control subjects. *Arch Gen Psychiatry* 1981; 38:175-179
17. Cornblatt BA, Lenzenweger MF, Dworkin RH, et al: Positive and negative schizophrenic symptoms, attention, and information processing. *Schizophr Bull* 1985; 11:397-408
18. Goldberg E, Costa LD: Hemispheric differences in the acquisition and use of descriptive systems. *Brain Lang* 1981; 14:144-173
19. Keefe RSE, McIs RC, Losonczy MF, et al: Characteristics of very poor outcome schizophrenia. *Am J Psychiatry* 1987; 144:889-895

Symptoms and Treatment Responses of Generalized Anxiety Disorder Patients With High Versus Low Levels of Cardiovascular Complaints

Rudolf Hoehn-Saric, M.D., Daniel R. McLeod, Ph.D., and Wesley D. Zimmerli, B.S.

Clinical observations suggest that patients with generalized anxiety disorder differ in somatic symptoms. The authors compared 28 patients with generalized anxiety disorder who had high levels of cardiovascular complaints with 32 patients with generalized anxiety disorder who had low levels of cardiovascular complaints on rating instruments, physiological measures, and use of anxiolytic medication. The two groups differed on somatic but not psychic symptoms on rating instruments. Patients with high levels of cardiovascular symptoms had higher levels of cardiac lability and required higher doses of alprazolam. These findings suggest that anxious patients with comparable levels of psychic anxiety may differ in levels of physical symptoms.

(Am J Psychiatry 1989; 146:854-859)

The definition of generalized anxiety disorder in DSM-III-R stresses common features but fails to provide a sense of the diversity seen in clinical practice. Several studies (1-9) have shown that anxiety may not be a unidimensional phenomenon. Analyzing symptoms reported by anxiety patients, Hamilton (3) found two factors that he called psychic and somatic anxieties. His findings were confirmed in a group of non-psychotic psychiatric patients by Buss (2) and in a general sample by Barratt (1). Schwartz et al. (6) argued that these factors represent processes which may need to be understood and addressed clinically as separate, albeit interacting, entities.

Not only do patients with generalized anxiety disorder differ considerably in psychic and somatic factors, but each factor may be affected differentially by psychological interventions. Schwartz et al. (6) found that anxious persons engaged in physical exercise

classes reported more cognitive than somatic anxiety but that those who practiced passive meditation rated themselves equal on both dimensions. Norton and Johnson (5), who treated snake-phobic patients with yoga or progressive muscle relaxation, reported that subjects with high levels of cognitive anxiety responded better to yoga than to relaxation exercise. The opposite was true for persons with high somatic anxiety. Similar results were obtained by Tamaren et al. (7) in a group of students scoring differently on measures of cognitive and somatic anxieties.

Psychic and somatic anxieties may also respond differently to pharmacological interventions. We have found that the psychic symptoms of patients with generalized anxiety disorder respond better to imipramine and that the somatic symptoms of such patients respond better to alprazolam (4). Tyrer and Lader (9) studied two groups of chronically anxious patients—one suffering mainly from somatic anxiety and one suffering mainly from psychic anxiety. They found that diazepam was more effective than placebo in both groups but that propranolol was superior to placebo only in the group with somatic anxiety, not in the group with psychic anxiety.

Most studies treat somatic anxiety as a uniform component of anxiety without distinguishing among patients with different types of somatic symptoms. Although patients with anxiety exhibit a mixture of somatic symptoms, clinical observations (10) suggest that muscular, cardiopulmonary, gastrointestinal, or genitourinary symptoms frequently dominate the clinical picture.

We were impressed by the fact that some of our patients with generalized anxiety disorder complained of a considerable degree of palpitations and increased perspiration but that other patients, who expressed comparable degrees of psychic anxiety, experienced few cardiopulmonary symptoms but complained predominantly of increased muscular tension and insomnia.

The aim of this study was to examine, in a sample of patients with generalized anxiety disorder, whether 1) the severity of somatic symptoms varies independently of the severity of psychic symptoms, 2) some somatic symptoms, such as cardiovascular symptoms, vary independently of other somatic symptoms, 3) patients

Received April 21, 1987; revisions received May 31, 1988, and Jan. 11, 1989; accepted Feb. 2, 1989. From the Department of Psychiatry, Johns Hopkins School of Medicine. Address reprint requests to Dr. Hoehn-Saric, 115 Meyer Bldg., Johns Hopkins Hospital, Baltimore, MD 21205.

Supported in part by NIMH grant MH-35435 and by a grant from the Upjohn Company, Kalamazoo, Mich.

Copyright © 1989 American Psychiatric Association.

who differ in cardiovascular symptoms also differ in heart rate and heart rate variability, and 4) patients who differ in cardiovascular symptoms require different types and levels of anxiolytic medication. Imipramine and alprazolam were chosen on the assumption that all patients would respond to alprazolam but that only patients with high levels of cardiovascular complaints, which may be etiologically related to panic disorder (11, 12), would respond to imipramine.

METHOD

Patients were included in the study if they were diagnosed as suffering from generalized anxiety disorder according to *DSM-III-R* and scored 18 or above on the Hamilton Rating Scale for Anxiety (3), 8 or above on the Covi Anxiety Scale (13), 5 or below on the Raskin Depression Scale (13), and 38 or above on the trait form of the State-Trait Anxiety Inventory (14). Patients with major mental illness, a history of psychosis, or a history of recent substance abuse were excluded. Patients had to have been free of all psychotropic medication for at least 2 weeks before participating in the study. Sixty patients were included in the total sample.

An attempt was made to include equal numbers of patients with high and low levels of cardiovascular complaints in the study. By using a score of 2 or above on the cardiovascular subscale of the Hamilton anxiety scale (3) as a criterion for a high level of cardiovascular complaints, the sample of 60 patients was divided into 28 patients with high levels of cardiovascular complaints and 32 patients with low levels of cardiovascular complaints. The cutoff score of 2 or above was chosen to ensure that the group with low levels of cardiovascular complaints contained patients without or with only mild cardiovascular complaints and the group with high levels of cardiovascular complaints contained patients with moderate to extreme cardiovascular complaints. All patients signed an informed consent form approved by the Joint Committee on Clinical Investigation.

Four rating scales that included somatic symptoms were administered: 1) the Hamilton anxiety scale (3), which differentiates between psychic and somatic symptoms, 2) the Hopkins Symptom Checklist-90 (HSCL-90) (15), which has five subscales that record psychic symptoms and four subscales (anxiety, depression, somatization, and sleep difficulties) that record somatic symptoms or a mixture of somatic and psychic symptoms, 3) the Somatic Symptoms Scale (16), and 4) a global rating of generalized anxiety. Scales that contained only psychic symptoms were the state and trait forms of the State-Trait Anxiety Inventory (14) and the Affects Balance Scale (17). The Hamilton and global scales were rated by an investigator; the remaining scales were completed by the patients.

As part of a drug response study to be reported elsewhere, heart interbeat interval recordings were obtained every 200 msec for 5-minute periods before and

1 hour after a single oral dose of 0.5 mg of alprazolam or 25 mg of imipramine. Both medications were tested at the same time interval after ingestion to maintain the double-blind design. The two drugs were assigned randomly within the groups with high and low levels of cardiovascular complaints. Recordings were taken while the patient sat in a comfortable reclining chair in a dimly lit room. Baseline values were calculated from the last 5 minutes of a 15-minute recording. To assess within-subject variability, variance in heart interbeat interval was obtained from the 200-msec sampling points. Because trends in heart interbeat interval occur over time, variance was estimated by means of the mean square successive difference statistic (18). Details of the recording procedures have been described by McLeod et al. (19).

The clinical effects of treatment on the total sample of patients have been described elsewhere (4). Patients continued to take the medications they had received during the psychophysiological examination for 6 weeks. The double-blind design was preserved. During the first week the dose was fixed at three capsules a day (1.5 mg/day of alprazolam or 75 mg/day imipramine). During the subsequent 5 weeks the dose was adjusted according to the clinical judgment of the investigators within a range of 1 to 12 capsules a day. Patients were required to remain on the same dose between the weekly visits.

RESULTS

The mean age of the patients was 41.3 years (range=23–60), and their mean level of education was 14.7 years (range=8–28). Thirty-five were women and 25 were men. Fifty-three were white and seven were black. No significant differences between the two groups in demographic data were found.

Correlations between the Hamilton cardiovascular subscale, by which the groups with high and low levels of cardiovascular complaints were initially differentiated, and each of the rating scales were examined by means of Spearman correlation coefficients. None of the correlations between the cardiovascular subscale of the Hamilton anxiety scale and scales containing only psychic items were significant (State-Trait Anxiety Inventory, trait: $r_s=0.11$; State-Trait Anxiety Inventory, state: $r_s=0.09$; Affects Balance Scale, index: $r_s=-0.21$). On the other hand, all correlations between the cardiovascular subscale of the Hamilton anxiety scale and the scales containing somatic items were significant ($p<0.01$) (Hamilton anxiety scale: $r_s=0.73$; Somatic Symptoms Scale: $r_s=0.49$; HSCL-90: $r_s=0.39$).

Table 1 provides a comparison of the rating scale scores of the two groups of subjects. A multivariate analysis (Hotelling's T^2) was followed by t tests adjusted by the Bonferroni method. Both methods of analysis revealed significant differences between the patients with high and low levels of cardiovascular complaints on the scales containing somatic items: the

TABLE 1. Rating Scale Scores of Patients With Generalized Anxiety Disorder Who Had High (N=28) or Low (N=32) Levels of Cardiovascular Complaints

Scale	Patients With High Complaint Levels		Patients With Low Complaint Levels		Analysis		
	Mean	SD	Mean	SD	t (df=58)	Bonferroni t ^a	Significance
Scales with somatic items ^b							
Hamilton anxiety scale	29.1	3.7	23.1	2.9	7.01	3.35	p<0.01
HSCL-90	117.5	62.3	75.8	37.0	3.09	2.80	p<0.05
Somatic Symptoms Scale	23.4	12.1	15.1	8.4	3.11	2.80	p<0.05
Global anxiety rating	2.9	0.3	2.6	0.5	3.59	3.35	p<0.01
Scales with only psychic items ^c							
State-Trait Anxiety Inventory							
Trait form	56.8	10.6	53.8	8.5	1.18	2.80	n.s.
State form	51.8	10.6	50.3	9.5	0.59	2.80	n.s.
Affects Balance Scale, index	-0.4	1.0	0.2	1.0	2.32	2.80	n.s.

^aCorrected for seven t tests performed. For nonsignificant comparisons, t corresponding to $\alpha=0.05$ is provided.

^bHotelling's $T^2=56.46$, $F=13.38$, $df=4, 55$, $p<0.0000$.

^cHotelling's $T^2=5.59$, $F=1.8$, $df=3, 56$, n.s.

Hamilton anxiety scale (rated 1 week after the initial rating that defined the two groups), the HSCL-90, the Somatic Symptoms Scale, and the global rating of anxiety. Patients with high levels of cardiovascular complaints scored consistently higher than patients with low levels of cardiovascular complaints on these scales. Scales containing only psychic items—the state and trait forms of the State-Trait Anxiety Inventory and the Affects Balance Scale—failed to differentiate the two groups.

The subscales of the Hamilton anxiety scale, the HSCL-90, the Somatic Symptoms Scale, and the Affects Balance Scale were examined next for differences between the groups with high and low levels of cardiovascular complaints. Table 2 shows subscales that contain predominantly somatic symptoms. Two subscales of the HSCL-90 that contain both psychic and somatic items (mixed subscales) are provided also. On the Somatic Symptoms Scale, only cardiopulmonary symptoms and sleep difficulty significantly differentiated the two groups. Similar results were found with the Hamilton anxiety scale, on which only scores for cardiovascular and respiratory symptoms were higher in the group with high levels of cardiovascular complaints than in the group with low levels of cardiovascular complaints. On the HSCL-90, the rating for somatization, a factor that contains a variety of somatic symptoms, was higher in the group with high levels of cardiovascular complaints, as were ratings of sleep difficulty.

Two subscales of the HSCL-90—the anxiety and depression subscales—contained both somatic and psychic items. The depression subscale failed to differentiate the two groups. However, the anxiety subscale, which contained the item heart pounding or racing, was higher in the group with high levels of cardiovascular complaints.

Table 2 also provides Spearman correlation coefficients for the correlation between the cardiovascular subscale of the Hamilton anxiety scale with each of the subscales listed. Significant correlations were found for

the cardiopulmonary, muscular, gastrointestinal-genitourinary, and sleep difficulty subscales of the Somatic Symptoms Scale; for the respiratory and insomnia subscales of the Hamilton anxiety scale; and for the somatization, sleep difficulty, and anxiety subscales of the HSCL-90.

None of the psychic subscales of the Hamilton anxiety scale, the HSCL-90, or the Affects Balance Scale differentiated the groups with high and low levels of cardiovascular complaints.

Cardiovascular measures were obtained on 48 patients, 21 in the group with high levels of cardiovascular complaints and 27 in the group with low levels of cardiovascular complaints. A three-way analysis of variance (Group by Drug by Time before and after medication for mean interbeat interval) showed a significant effect for Time ($F=4.16$, $df=1, 44$, $p<0.05$) but not for Drug. During the initial recording the two groups had similar mean interbeat intervals, corresponding to heart rates of 70.6 beats per minute for the group with high levels of cardiovascular complaints and 70.3 beats per minute for the group with low levels of cardiovascular complaints. During the second recording the group with high levels of cardiovascular complaints showed a significant increase in interbeat interval, but the group with low levels of cardiovascular complaints did not (see table 3). Interbeat interval variability (mean square successive difference) results were comparable. A three-way ANOVA showed an interaction between Time and Group ($F=7.33$, $df=1, 44$, $p<0.02$) but no Drug effect. Variability did not differentiate the two groups during the pre-drug session, but the group with high levels of cardiovascular complaints showed a significant increase in interbeat interval variability from the pre- to the post-drug recording. Although the mean interbeat interval was correlated with the interbeat interval mean square successive difference ($r_s=0.41$, $p<0.01$) and the cardiovascular subscale of the Hamilton anxiety scale was correlated with the cardiopulmonary subscale of the Somatic Symptoms Scale ($r_s=0.63$, $p<0.01$), the phys-

TABLE 2. Subscale Scores of Patients With Generalized Anxiety Disorder Who Had High (N=28) or Low (N=32) Levels of Cardiovascular Complaints

Scale and Subscale	Patients With High Complaint Levels		Patients With Low Complaint Levels		Analysis		
	Mean	SD	Mean	SD	t (df=58)	Bonferroni r^a	r_s^b
Somatic subscales							
Somatic Symptoms Scale ^c							
Cardiopulmonary subscale	1.0	0.5	0.4	0.6	4.10	3.25 ^d	0.65 ^d
Muscular subscale	1.2	0.5	0.8	0.6	1.84	2.66	0.37 ^d
Headache subscale	1.4	1.0	1.5	0.6	0.44	2.66	0.08
Gastrointestinal-genitourinary subscale	0.9	0.5	0.6	0.6	1.98	2.66	0.31 ^e
Sleep difficulty subscale	2.1	1.0	1.3	1.1	3.60	3.25 ^d	0.28 ^e
Hamilton anxiety scale ^f							
Cardiovascular subscale	2.2	0.5	0.5	0.6	9.59	3.46 ^d	
Respiratory subscale	2.2	0.5	1.6	0.6	4.99	3.46 ^d	0.49 ^d
Muscular subscale	1.9	1.0	2.2	1.1	1.55	2.89	0.05
Gastrointestinal subscale	1.9	1.0	1.6	1.1	1.06	2.89	0.17
Genitourinary subscale	2.0	1.0	1.9	0.6	0.48	2.89	0.04
Autonomic subscale	2.2	0.5	1.9	0.6	1.76	2.89	0.03
Insomnia subscale	2.4	0.5	1.8	1.1	2.43	2.89	0.25 ^e
HSCL-90 ^g							
Somatization subscale	1.2	1.0	0.7	0.6	3.00	2.92 ^e	0.51 ^d
Sleep difficulty subscale	2.5	1.0	1.3	1.1	4.64	3.47 ^d	0.41 ^d
Subscales with somatic and psychic items							
HSCL-90 ^g							
Anxiety subscale	1.6	1.0	1.0	0.6	3.26	2.92 ^e	0.44 ^d
Depression subscale	1.5	1.0	1.1	0.6	2.07	2.92	0.14

^aCorrected for number of t tests performed (equal to number of subscales on each scale). For nonsignificant comparisons, t corresponding to $\alpha=0.05$ provided.

^bCorrelation with cardiovascular subscale of the Hamilton anxiety scale.

^cFive t tests performed.

^d $p<0.01$.

^e $p<0.05$.

^fNine t tests performed.

^gTen t tests performed.

TABLE 3. Heart Interbeat Intervals and Drug Doses of Patients With Generalized Anxiety Disorder Who Had High or Low Levels of Cardiovascular Complaints

Item	Patients With High Complaint Levels			Patients With Low Complaint Levels			Analysis		
	N	Mean	SD	N	Mean	SD	t	df	Significance
Interbeat interval (msec)									
Baseline	21	850.1	121.4	27	853.5	133.4	0.08	46	n.s.
Change score ^a	21	70.5 ^b	100.8	27	16.3 ^c	78.6	2.09	46	$p<0.05$
Interbeat interval variability (msec)									
Baseline	21	746.2	809.9	27	1033.6	1040.4	0.08	46	n.s.
Change score ^a	21	353.9 ^c	731.0	27	-178.1	631.7	2.70	46	$p<0.01$
Alprazolam dose (mg/day)									
Week 2 of drug administration	12	2.1	0.7	12	1.9	0.9	0.60	22	n.s.
Week 6 of drug administration	12	2.8 ^d	1.3	12	1.8	0.9	2.30	22	$p<0.03$
Imipramine dose (mg/day)									
Week 2 of drug administration	11	66.7	19.2	15	78.2	25.2	1.27	24	n.s.
Week 6 of drug administration	11	86.4	40.5	15	88.6	44.8	0.13	24	n.s.

^aDifference between values obtained during morning and early afternoon.

^b $t=3.21$, $df=40$, $p<0.005$.

^c $t=2.22$, $df=40$, $p<0.04$.

^d $t=2.57$, $df=22$, $p<0.03$.

iological measures were not correlated with scores on the rating scales.

Table 3 also presents the average daily alprazolam and imipramine doses for the groups with high and low levels of cardiovascular complaints. Data were available for the 50 patients who completed 6 weeks of

a double-blind drug trial. During the second week on medication both groups receiving alprazolam took comparable levels of the drug. By week 6, however, the patients with high levels of cardiovascular complaints were taking significantly more alprazolam than the patients with low levels of cardiovascular complaints.

There were no group differences in imipramine dose at either week 2 or week 6.

DISCUSSION

Our study supports previous reports (1–4) that psychic and somatic anxieties are clinically separate, albeit interacting, entities. By dividing patients with generalized anxiety disorder according to the severity of their cardiovascular symptoms we were able to obtain groups who had high and low levels of somatic anxiety but similar levels of psychic anxiety. This division was further supported by the lack of correlation between the cardiovascular subscale of the Hamilton anxiety scale and the anxiety scales that do not contain somatic symptoms. Thus, the severity of psychic anxiety did not necessarily correspond to the severity of physical anxiety symptoms. In addition, we were able to demonstrate that individual somatic symptoms may vary independently of each other. Our two groups of patients differed on cardiovascular and respiratory symptoms but not on muscular tension, headaches, gastrointestinal distress, or genitourinary symptoms. The cardiovascular subscale of the Hamilton anxiety scale intercorrelated only with subscales of the Hamilton anxiety scale that describe respiratory symptoms and sleep disturbances. Although it correlated with muscular and gastrointestinal-genitourinary symptoms on the Somatic Symptoms Scale, these correlations were generally low. The differences in correlations obtained on the two scales can be attributed to differences in the wording of items or to differences in the interpretation of symptoms by patients and raters. Although these discrepancies need further examination, the overall results support the observation by Weiner (10) that somatic symptoms of anxiety do not constitute a global expression of the severity of anxiety but may differ according to individual predisposition. Thus, somatic symptoms should be examined not only as single factors but in functional subdivisions as well. The fact that investigators' ratings were confirmed by patients' self-ratings increased the validity of the findings.

Self-reports of somatic symptoms have failed to correspond with patients' actual physiological states (20). This was also the case in this study; subjective ratings of cardiovascular symptoms and physiological measures of heart activity failed to correlate with each other. Tyrer (8), who divided his anxiety patients on the basis of "subjective interpretation of symptoms" into somatic and psychic anxiety groups, found no physiological differences between the two groups. However, he reported a high correlation between self-ratings and physiological measures in the somatic anxiety group but a low correlation in the psychic anxiety group. He concluded that "somatically oriented patients have a greater awareness of physiological changes" and that patients with psychic symptoms tend to disregard bodily feelings. Our findings suggest

that the differences between the two groups may consist not only of psychological differences but of physiological differences as well. Thus, it appears that psychological and physiological factors contribute to self-reported differences in cardiovascular symptoms.

Differences in perception of somatic symptoms may also influence the response to pharmacotherapy. Tyrer (8) found that patients with somatic but not psychic anxiety responded more to propranolol than to placebo. We have shown that alprazolam affects predominantly somatic symptoms whereas imipramine affects predominantly psychic symptoms (4). Although we failed to find qualitatively different drug effects between the groups in the current study, we observed that the group with high levels of cardiovascular complaints required significantly higher levels of alprazolam than the group with low levels of cardiovascular complaints. No differences between the groups were found for imipramine levels. It is unlikely that this difference in alprazolam levels between patients with high and low levels of cardiovascular complaints was due to investigator bias. Although the investigators were not blind regarding the assignment of their patients to the groups with high and low levels of cardiovascular complaints, they were blind to the type of medication prescribed. If bias were the reason for the group difference in dosage, the group with high levels of cardiovascular complaints would have received higher levels of both alprazolam and imipramine than the group with low levels of cardiovascular complaints. This was not the case. The use of medication by the groups with high and low levels of cardiovascular complaints corresponded to that expected in patients with comparable levels of psychic symptoms but different levels of cardiovascular symptoms (4).

In conclusion, our findings demonstrate the need to register psychic and somatic symptoms as well as symptom subgroups when examining and treating patients with generalized anxiety disorder. Further studies are needed to examine the degree to which bodily feelings correspond to a mental set and to actual physiological states and response patterns.

REFERENCES

1. Barratt ES: Anxiety and impulsiveness: toward a neurophysiological model, in *Anxiety: Current Trends in Theory and Research*, vol 1. Edited by Spielberger CD. New York, Academic Press, 1972
2. Buss AH: Two anxiety factors in psychiatric patients. *J Abnorm Soc Psychol* 1962; 65:426–427
3. Hamilton M: The assessment of anxiety states by rating. *Br J Med Psychol* 1959; 32:50–55
4. Hoehn-Saric R, McLeod DR, Zimmerli WD: Differential effects of alprazolam and imipramine in generalized anxiety: somatic vs psychic symptoms. *J Clin Psychiatry* 1988; 49:293–301
5. Norton GR, Johnson WE: A comparison of two relaxation procedures for reducing cognitive and somatic anxiety. *J Behav Ther Exp Psychiatry* 1983; 14:209–214
6. Schwartz GE, Davidson FJ, Coleman DJ: Patterning of cognitive and somatic processes in the self-regulation of anxiety: effects of meditation versus exercise. *Psychosom Med* 1978; 40: 321–328

7. Tamaren AJ, Carney RM, Allen TW: Predictive validity of the cognitive vs somatic anxiety distinction. *Pavlovian J Biol Sci* 1985; 20:177-180
8. Tyrer P: *The Role of Bodily Feelings in Anxiety*. London, Oxford University Press, 1967
9. Tyrer PJ, Lader MH: Response to propranolol and diazepam in somatic and psychic anxiety. *Br Med J* 1974; 2:14-16
10. Weiner H: The psychobiology and pathophysiology of anxiety and fear, in *Anxiety and Anxiety Disorders*. Edited by Tuma AH, Maser J. Hillsdale, NJ, Lawrence Erlbaum Associates, 1985
11. Cloninger CR, Martin RL, Clayton P, et al: A blind follow-up and family study of anxiety neurosis: preliminary analysis of the St Louis 500, in *Anxiety: New Research and Changing Concepts*. Edited by Klein DF, Rabkin JG. New York, Raven Press, 1981
12. Sheehan D: Strategies for diagnosis and treatment of anxiety disorders, in *Diagnosis and Treatment of Anxiety Disorders*. Edited by Pasnau RO. Washington, DC, American Psychiatric Press, 1984
13. Covi L, Lipman RS, McNair D, et al: Symptomatic volunteers in multicenter drug trials. *Prog Neuropsychopharmacol* 1979; 3: 521-533
14. Spielberger CD, Gorsuch RL, Lushene RD: *STAI Manual*. Palo Alto, Calif, Consulting Psychologists Press, 1970
15. Lipman RS, Covi L, Shapiro AK: The Hopkins Symptom Checklist (HSCL) factors derived from the HSCL-90. *J Affective Disord* 1979; 1:9-24
16. Hoehn-Saric R: Characteristics of chronic anxiety patients, in *Anxiety: New Research and Changing Concepts*. Edited by Klein DF, Rabkin JG. New York, Raven Press, 1981
17. Derogatis LR, Meyer JK, Vazquez N: The psychological profile of the transsexual. *J Nerv Ment Dis* 1978; 166:234-254
18. Heslegrave RJ, Ogilvie JC, Furedy JJ: Measuring baseline-treatment differences in heart rate variability: variance versus successive difference mean square and beats per minute versus interbeat intervals. *Psychophysiology* 1979; 16:151-157
19. McLeod DR, Hoehn-Saric R, Labib AS, et al: Six weeks of diazepam treatment in normal women: effects on psychomotor performance and psychophysiology. *J Clin Psychopharmacol* 1988; 8:83-99
20. McLeod DR, Hoehn-Saric R, Stefan RI: Somatic symptoms of anxiety: comparison of self-report and physiological measures. *Biol Psychiatry* 1986; 21:301-310

Relapse and Rebound Following Discontinuation of Benzodiazepine Treatment of Panic Attacks: Alprazolam Versus Diazepam

Peter P. Roy-Byrne, M.D., Stephen R. Dager, M.D., Deborah S. Cowley, M.D.,
Peter Vitaliano, Ph.D., and David L. Dunner, M.D.

The authors assessed the effects of partial tapering followed by abrupt discontinuation of alprazolam, diazepam, and placebo in 40 patients with panic attacks. The anxiety scores and frequency of panic attacks of the three groups did not differ at the end of the initial 2-week taper, but 1 week after abrupt discontinuation of the remaining medication, patients formerly taking alprazolam had greater increases in anxiety but no more panic attacks than did the other patients. Because of low statistical power, differences in benzodiazepine half-lives, absence of multiple ratings, and imbalances between groups in clinical characteristics, these findings must be viewed as preliminary.

(Am J Psychiatry 1989; 146:860-865)

The clinical deterioration that often follows discontinuation of benzodiazepine treatment in anxious patients is a phenomenon that has been widely reported but less well studied. Such deterioration is often globally labeled as withdrawal but actually consists of three related phenomena: relapse (reemergence of the original anxiety state), withdrawal (the occurrence of "new," time-limited symptoms that were not present as part of the original anxiety state and begin and end depending on the pharmacokinetics of the benzodiazepine), and rebound (an increase in anxiety above original baseline levels that may be a combination of relapse and withdrawal) (1).

Separation of these three phenomena is often difficult, and many earlier studies made no attempt to do this. Although more recent studies of benzodiazepine withdrawal have used specialized scales to detect "new" symptoms (2) and more frequent ratings to de-

tect time-limited symptoms (3), it is still unclear whether complete separation of relapse, rebound, and withdrawal is possible.

The majority of studies of benzodiazepine "withdrawal" have considered mixed diagnostic groups of anxious patients and found that withdrawal reactions are more likely if benzodiazepines have been used for more than 8 months, if discontinuation is abrupt rather than tapered, if the drug has a short half-life, and if the patient has a pathological premorbid personality style (1). More recently (4, 5), a high incidence (60%-80%) of withdrawal has been reported in two case series of patients with panic disorder taking alprazolam for less than 8 months. A more recent and much larger study (6) reported a somewhat lower incidence (30%) of withdrawal in patients who had used alprazolam for less than 8 weeks, although this figure is larger than that reported with short-term use of other benzodiazepines in mixed groups of anxious patients (1). Since previous studies have not examined withdrawal from other benzodiazepines in homogeneous groups of patients with panic disorder, it is unclear whether these findings are due to a greater vulnerability to withdrawal in patients with panic disorder or to the unique triazolobenzodiazepine structure of alprazolam. A recent study (7) suggesting that alprazolam shows an unusual relationship between brain concentration and benzodiazepine receptor occupancy at low concentrations provides a theoretical rationale for a potential difference between alprazolam and other benzodiazepines.

To clarify this issue, we compared response to drug discontinuation in patients with panic attacks who were randomly assigned to treatment for 6 weeks with alprazolam, diazepam, or placebo. This study did not provide data to measure "new" symptoms, nor were ratings obtained during the course of taper. Therefore, this design cannot distinguish relapse and rebound reactions from "true" withdrawal. Nonetheless, by assessing the relative change in symptoms of anxiety and panic in patients with panic disorder withdrawn from alprazolam, diazepam, or placebo, it sheds light on anecdotal claims that withdrawal from a triazoloben-

Received June 27, 1988; revision received Dec. 1, 1988; accepted Jan. 9, 1989. From the Department of Psychiatry and Behavioral Sciences, University of Washington and Harborview Medical Center, Seattle. Address reprint requests to Dr. Roy-Byrne, University of Washington, Department of Psychiatry, RP-10, Seattle, WA 98195.

Funded by a grant from the Upjohn Company, Kalamazoo, Mich. The authors thank Carl Lewis, M.D., for thoughtful comments and suggestions.

Copyright © 1989 American Psychiatric Association.

zodiazepine as opposed to other benzodiazepines is more likely to cause worsening symptoms of anxiety.

METHOD

Patients were participants in a double-blind study of the comparative efficacy of alprazolam versus diazepam versus placebo in a mixed group of anxious patients (8). The 88 patients who originally entered this study were diagnosed according to *DSM-III* criteria: 49 patients had panic disorder (all but one of these were included in the previously published report [8]), 16 had generalized anxiety with infrequent panic attacks, and 23 had "pure" generalized anxiety.

Because of evidence that patients with infrequent panic attacks resemble those with panic disorder in age at onset (9), symptom profile (9), lactate responsivity (10, 11), and clinical characteristics (10), we included in this study all 71 patients who had panic attacks at baseline or during the treatment phase of the study regardless of the frequency of panic attacks. Specifically, this group comprised the 49 patients with panic disorder, the 16 patients with panic attacks too infrequent to meet criteria for panic disorder at baseline, and six of the 23 patients originally diagnosed as having generalized anxiety disorder who had panic attacks during the early part of the treatment phase. Panic attacks were assessed by psychiatrists at weekly interviews and met full *DSM-III* criteria.

The tablets used in the study contained 1 mg of alprazolam, 10 mg of diazepam, or placebo and were administered three times a day with titration until side effects intervened. Patients were assessed at week 1 (following 1 week of placebo washout) and at weeks 2, 3, 5, and 7 during the course of treatment. At week 7, the mean \pm SD number of pills taken by the placebo group (7.5 ± 2.9) was significantly greater than that taken by the patients given alprazolam (4.3 ± 2.8) or diazepam (5.6 ± 3.1) ($F=4.2$, $df=2, 37$, $p<0.03$).

Following week 7, tablets for each treatment group were tapered gradually over the next 2 weeks at a rate of one every 3 to 5 days. The rates of taper were not significantly different in the three groups ($F=0.46$, $df=2, 36$). By week 9, the mean number of tablets for the three groups had been reduced by approximately half (alprazolam= 2.4 ± 1.2 , diazepam= 2.9 ± 1.6 , placebo= 4.7 ± 3.6) ($F=3.5$, $df=2, 37$, $p<0.05$). At week 9, placebo replaced active medication under single-blind conditions. The taper off placebo was completed by week 10. Patients were assessed at week 9 (taper approximately half complete) and week 10 (1 week after abrupt discontinuation of active medication). During this last week all patients continued to take capsules, although a smaller number than during treatment. Thus, they were aware that their drug was being decreased but not that it had been discontinued at week 9.

Of the 71 patients with panic attacks who entered the study, 31 dropped out between weeks 1 and 9. The relative dropout rates for each group before and after

taper were compared by using chi-square analyses to the proportions expected by the relative durations of these conditions (6 and 3 weeks) to determine whether dropout was more likely to occur during taper or discontinuation and whether it might constitute a measure of withdrawal. In addition, dropout rates during taper were compared among the three groups to determine if a particular drug was associated with higher dropout rates during taper, which would suggest that withdrawal may have been more difficult for this group.

Forty patients completed the trial: 13 patients treated with alprazolam, 15 patients treated with diazepam, and 12 patients given placebo. Two of the twelve placebo patients were rated only at week 9, so the placebo cell size for week 10 is 10. There were four patients with agoraphobia in the alprazolam group and one each in the diazepam and placebo groups. Patients ranged in age from 19 to 63 years (mean \pm SD= 33.1 ± 9.9). There were 14 men and 26 women. The distributions of age ($F=0.31$, $df=2, 37$) and sex ($F=1.8$, $df=2, 37$) in the three groups were not significantly different.

The major assessments at each week were Hamilton Rating Scale for Anxiety (12) scores and frequency of panic attacks. Because response to treatment was not the primary focus of this report and also to minimize the number of post hoc tests performed, scores at weeks 2, 3, and 5 were averaged to yield five time points for analysis: week 1; the mean of weeks 2, 3, and 5; week 7; week 9; and week 10. A split-plot analysis of variance (ANOVA) (between and within groups) was performed on the Hamilton anxiety scale scores, and subsequent between- and within-group analyses over time were used to compare relapse and rebound among the three groups. Between-group analyses were performed at the different time points to compare the three groups during treatment and withdrawal, and within-group analyses were performed to look for treatment and withdrawal effects in the individual groups. Because the distribution of panic attacks was skewed, a nonparametric (repeated measures) Friedman's test was performed on frequency of panic attacks over time to assess therapeutic efficacy and withdrawal in the individual groups. Kruskal-Wallis one-way ANOVAs were also performed to compare the frequency of attacks in the three groups at the various time points.

We also compared the frequency of individual relapse and rebound across the groups at weeks 9 and 10 using chi-square analyses (or Fisher's exact test for cell frequencies less than 5). Individual relapse was defined as 1) a 50% increase in Hamilton anxiety scale score over week 7 (to parallel traditional definitions of anxiolytic response as a 50% reduction) and an absolute increase in Hamilton anxiety scale score of at least 5 points over week 7 to control for high percentage increases due to low scores at week 7 and 2) an increase in panic attacks at weeks 9 and 10 over week 7. Individual rebound was defined as 1) a 10% increase in Hamilton anxiety scale scores over week 1, in keeping

with a previously published study of rebound (13), and 2) an increase in panic attacks over week 1. Comparisons using the placebo group were performed to control for clinical deterioration due to drug discontinuation and loss of pharmacological effect and/or withdrawal versus deterioration due to perceived reduction in number of pills taken.

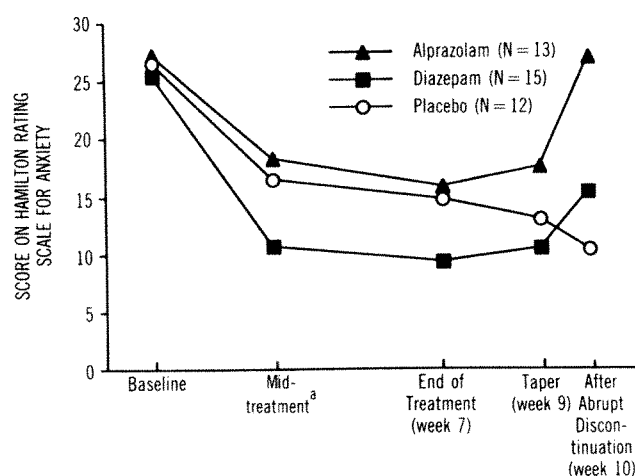
Finally, because any observed increases in anxiety or panic attacks during discontinuation might partially reflect frequency of panic attacks before either treatment or remission of symptoms, we examined relapse as a function of certain clinical characteristics of patients before discontinuation. Since the cell sizes of treatment groups dichotomized by various characteristics were too small for statistical analysis, frequency of relapse was determined for heuristic purposes in patients with panic disorder ($N=23$) compared with patients with infrequent panic ($N=17$); patients remitted (no panic attacks) at week 7 ($N=24$) compared with those who still had panic attacks ($N=16$); and patients who had more (four or more) ($N=21$) or fewer (three or fewer) ($N=19$) panic attacks per week than the median number for all three groups. Week 10 data were used for all patients except for the two placebo patients who had ratings for only week 9.

RESULTS

Dropout rates over the entire study were similar in all three groups (11 [46%] of 24 in the alprazolam group, seven [32%] of 22 in the diazepam group, and 13 [52%] of 25 in the placebo group) ($\chi^2=2.0$, $df=2$). Dropout rates during taper (3-week duration) compared with active treatment (6-week duration) were not significantly different from the 33% rate expected by chance and also were not significantly different among the three groups (four [36%] of 11 for the alprazolam group; one [14%] of seven for the diazepam group; five [38%] of 13 for the placebo group) ($\chi^2=1.3$, $df=2$). Thus, in this study, discontinuation did not contribute to dropout rates any more than did other events occurring during the treatment phase, such as nonresponse or side effects.

The ANOVA on Hamilton anxiety scale scores revealed a significant Group by Time interaction ($F=5.7$, $df=2$, 35 , $p<0.001$), suggesting that the groups changed differentially. Time tests for the three separate groups revealed that they all improved with treatment (for the alprazolam group, $F=26.6$, $df=2$, 24 , $p<0.001$; for the diazepam group, $F=32.6$, $df=2$, 28 , $p<0.001$; for the placebo group, $F=10.1$, $df=2$, 22 , $p<0.001$). The results of these tests were still significant even after correcting for deviations from lack of compound symmetry in the covariance matrix of the repeated measures (14). Although none of the three groups showed any change in anxiety during taper, both the alprazolam and diazepam groups showed an increase in anxiety following abrupt discontinuation at week 10 ($p=0.03$ and $p=0.045$, Sheffé, respectively).

FIGURE 1. Anxiety Scores During Discontinuation of Alprazolam, Diazepam, or Placebo of Patients With Panic Attacks



^aMean of weeks 2, 3, and 5.

Between-group analyses showed that there were no differences at the start ($F=0.2$, $df=2$, 37) or end ($F=1.9$, $df=2$, 37) of treatment, although patients in the diazepam group responded earlier and were significantly more improved at mid-treatment than the alprazolam group ($F=5.0$, $df=2$, 37 , $p<0.02$; $p=0.02$, Scheffé) (see figure 1). Following the 2-week taper, the Hamilton anxiety scale scores of the three groups were not significantly different ($F=1.5$, $df=12$, 36), but 1 week after abrupt discontinuation the alprazolam group had significantly higher scores than the diazepam and placebo groups ($F=7.3$, $df=2$, 35 , $p<0.002$; $p=0.03$ and $p=0.004$, Scheffé, respectively).

There was a reduction in panic attacks with both alprazolam ($\chi^2=4.6$, $df=2$, $p<0.10$) and diazepam ($\chi^2=6.4$, $df=2$, $p<0.05$) but not placebo ($\chi^2=1.6$, $n.s.$) (Friedman's test). In contrast to the results with Hamilton anxiety scale scores, there was no statistically significant increase in panic attacks in any of the groups following taper and abrupt withdrawal (alprazolam, $\chi^2=1.6$; diazepam, $\chi^2=3.4$; placebo, $\chi^2=1.7$). Comparisons of the groups at the different time points showed no differences in frequency of attacks between groups at the beginning ($H=0.96$, $df=2$), middle ($H=4.35$, $df=2$), or end ($H=3.34$, $df=2$) of treatment; following taper ($H=3.74$, $df=2$); or following abrupt discontinuation ($H=0.46$, $df=2$).

Comparison of individual relapse rates supported these group analyses (see table 1). There were no significant differences among the groups following taper (week 9) in relapse rates as defined by changes in Hamilton anxiety scale score ($\chi^2=0.71$) and frequency of panic attacks ($\chi^2=1.1$). Following abrupt discontinuation (week 10), there was a significant difference among the groups ($\chi^2=8.7$, $df=2$, $p<0.02$): a significantly higher proportion of the patients treated with alprazolam than patients given placebo relapsed ac-

TABLE 1. Response of Patients With Panic Attacks to Tapering (Week 9) or Abrupt Discontinuation (Week 10) of Benzodiazepines or Placebo

Measure	Alprazolam				Diazepam				Placebo			
	Week 9 (N=13)		Week 10 (N=13)		Week 9 (N=15)		Week 10 (N=15)		Week 9 (N=12)		Week 10 (N=10)	
	N	%	N	%	N	%	N	%	N	%	N	%
Relapse												
50% increase over week 7 and absolute increase over week 7 in Hamilton anxiety scale scores	2	15	9	69	3	20	5	33	1	8	1	10
Increase over week 7 in panic attacks	3	23	6	46	2	13	5	33	1	8	1	10
Rebound												
10% increase over week 1 in Hamilton anxiety scale scores	1	8	6	46	1	7	1	7	1	8	1	10
Increase over week 1 in panic attacks	2	15	2	15	0	0	3	20	3	25	1	10

TABLE 2. Effect on Relapse Rates After Abrupt Discontinuation (Week 10)^a of Benzodiazepines or Placebo of Clinical Characteristics of Patients With Panic Attacks

Clinical Characteristic	Alprazolam					Diazepam					Placebo				
	N	Hamilton Criteria ^b		Panic Attacks ^c		N	Hamilton Criteria ^b		Panic Attacks ^c		N	Hamilton Criteria ^b		Panic Attacks ^c	
		N	%	N	%		N	%	N	%		N	%	N	%
Diagnosis of panic disorder	7	4	57	4	57	10	4	40	3	30	6	0	0	1	17
Infrequent panic attacks	6	5	83	2	33	5	1	20	2	40	6	1	16	0	0
Not remitted at week 7	5	3	60	3	60	4	1	25	1	25	7	1	14	1	14
Remitted at week 7	8	6	75	3	38	11	4	36	4	36	5	0	0	0	0
Four or more panic attacks per week	10	8	80	5	50	4	0	0	2	50	7	1	14	1	14
Three or fewer panic attacks per week	3	1	33	1	33	11	5	45	3	27	5	0	0	0	0

^aTwo placebo patients were rated at week 9 (during tapering).^b50% increase in Hamilton anxiety scale score over week 7 and absolute increase in score over week 7.^cIncrease over week 7 in panic attacks.

cording to their Hamilton anxiety scale scores ($p < 0.01$, Fisher's exact test, two-tailed). The proportion of patients who relapsed after receiving diazepam was intermediate and not significantly different from that of patients given either alprazolam or placebo. In contrast, the proportion of patients in the three groups who experienced increases in panic attacks at week 10 was not significantly different ($\chi^2 = 3.4$), although the figures in both drug groups (46% and 33%) were considerably higher than that in the placebo group (10%).

Comparison of individual rebound anxiety and panic attack rates also yielded a similar pattern of results (see table 1). Although there were no differences among the groups at week 9 in rebound as defined by higher-than-baseline Hamilton anxiety scale scores ($\chi^2 = 0.85$, $df = 2$, $p = 0.65$), or in the frequency of panic attacks ($\chi^2 = 3.9$, $df = 2$, $p = 0.15$) at week 10, the three groups differed in the proportion of patients with higher Hamilton anxiety scale scores ($\chi^2 = 10.29$, $df = 2$, $p < 0.005$). A significantly higher proportion of

alprazolam patients had rebound anxiety than did diazepam patients ($p < 0.03$, Fisher's exact test, two-tailed) or placebo patients ($p < 0.02$, Fisher's exact test, two-tailed). As with the findings for panic attack relapse, however, there was no significant difference among the groups in the proportion of patients with rebound panic attacks ($\chi^2 = 0.45$).

Table 2 provides data on relapse rates according to patients' clinical characteristics before drug or placebo discontinuation. Although these characteristics do not appear to contribute to relapse defined by increases in Hamilton anxiety scale scores (i.e., the rates are similar in patients with and without higher versus lower attack frequencies before discontinuation), they do appear to contribute to relapse defined by increases in the frequency of panic attacks. More specifically, the nonsignificantly higher relapse rates in the alprazolam (46%) versus the diazepam (33%) and placebo (10%) groups (table 1) appeared to be confined to patients who had had more panic attacks before discontinuation.

DISCUSSION

These findings suggest that there was little difference between groups when drugs were tapered to approximately half the original dose (week 9) but that 1 week after single-blind abrupt discontinuation of the remaining medication (week 10) there were greater increases in anxiety but not in the frequency of panic attacks in patients with panic disorder withdrawn from alprazolam than there were in patients withdrawn from diazepam or placebo. Furthermore, patients withdrawn from diazepam showed significant increases in anxiety following abrupt discontinuation in contrast to placebo patients, who showed no significant change.

Our failure to find differences at week 9 suggests that, during the initial tapering of benzodiazepine treatment in patients with panic disorder, there is little symptom exacerbation relative to that seen following abrupt discontinuation (week 10), despite patients' awareness of drug tapering. This is in agreement with the only study of alprazolam withdrawal in panic disorder which showed that anxiety increases were confined to the final stages of taper and 1 week thereafter (6), although abrupt discontinuation is not comparable to the final stages of a gradual taper. These findings reinforce the current clinical practice of tapering rather than abruptly discontinuing benzodiazepines.

The greater increases in anxiety 1 week after abrupt discontinuation of medication in patients taking alprazolam versus diazepam is noteworthy. These findings did not seem to be related to differences in clinical characteristics among the treatment groups before discontinuation. Similar findings regarding anxiety levels have been noted in two separate studies comparing diazepam with lorazepam (15) and bromazepam (13) in mixed groups of anxious patients. The relapse (15) and rebound (13) noted in these studies have been attributed to the shorter half-lives of lorazepam and bromazepam; in one study (13), relapse and rebound were present only in patients who had their drug abruptly discontinued rather than tapered. By week 10 of our study, blood levels of diazepam were probably greater than those of alprazolam because of the longer half-life of diazepam. Thus, it is possible that another week of ratings might have uncovered additional instances of withdrawal in diazepam patients.

Although there were no significant differences in frequency of panic attacks during discontinuation, the small cell sizes in these analyses, as well as the nonparametric statistics used, prevent detection of any but the most sizable differences (i.e., there is a greater probability of type II error). Thus, it must be noted that, although nonsignificant, the frequency of increases in panic attacks was 50% higher in patients who had been taking alprazolam than in those who had been taking diazepam and three times greater in patients who had been taking diazepam compared with those who had been taking placebo. This trend for increases in the frequency of panic attacks in the alprazolam

group appeared to be at least partly a function of the greater frequency of panic attacks in these patients at baseline and before discontinuation and suggests that these increases represent a return of panic attacks rather than a withdrawal syndrome.

Despite the greater incidence of increased anxiety following alprazolam withdrawal, these results stand in contrast to the finding of Fyer et al. (5) that 14 of 17 patients taking alprazolam were unable to complete a gradual taper. In the current study, only four of the 11 alprazolam patients who dropped out did so during taper, and it did not appear that failure to complete was due to withdrawal because a similar proportion of placebo patients dropped out at this point. Furthermore, the incidence of panic attack increases was fairly similar in both drug groups and comparatively lower than that observed in the Fyer et al. study (5). The design of our study, in which patients were switched to placebo capsules between weeks 9 and 10, may partly account for this difference. Pecknold et al. (16) showed that continued placebo treatment in anxious patients abruptly withdrawn from benzodiazepines may attenuate the reemergence of symptoms of anxiety. Thus, "withdrawal" symptoms in patients no longer taking pills is a combination of true withdrawal and "pseudo-withdrawal" (i.e., negative placebo response to perceived drug discontinuation).

It should also be noted that, despite randomization, the clinical features of the alprazolam and diazepam groups were not comparable. Although not statistically significant, in the diazepam group there were fewer patients with agoraphobia, fewer patients with four or more panic attacks per week during the study, and fewer patients who dropped out. In addition, diazepam patients appeared to respond more rapidly during the initial treatment phase. These findings all suggest that patients in the diazepam group who completed the study may have been different in certain ways from other patients who completed the study despite having comparatively high Hamilton anxiety scale scores at baseline.

Finally, Rickels et al. (15) suggested that weekly rating intervals are inadequate for detecting the full range of relapse, rebound, and withdrawal phenomena because symptom increases may be transient (several days) and go undetected with weekly assessments. Given this fact, it is possible that we might have missed important differences between weeks 7 and 9 and weeks 9 and 10. Thus, our finding that discontinuation of alprazolam treatment is associated with greater increases in anxiety than is discontinuation of diazepam must be regarded as tentative and followed up with a study in which the patient groups are more comparable and rating intervals are more frequent. Use of a similarly short half-life benzodiazepine as a comparison drug would also be important, since this would allow separation of the relative effects of half-life and triazolobenzodiazepine structure.

REFERENCES

1. Roy-Byrne P, Hommer D: Benzodiazepine withdrawal: overview and implications for the treatment of anxiety. *Am J Med* 1988; 84:1041-1050
2. Tyrer P, Owen B, Dawling S: Gradual withdrawal of diazepam after long-term therapy. *Lancet* 1983; 1:1402-1406
3. Rickels K, Fox IL, Greenblatt DJ, et al: Clorazepate and lorazepam: clinical improvement and rebound anxiety. *Am J Psychiatry* 1988; 145:312-317
4. Mellman TA, Uhde TW: Withdrawal syndrome with gradual tapering of alprazolam. *Am J Psychiatry* 1986; 143:1464-1466
5. Fyer AJ, Liebowitz MR, Gorman JM, et al: Discontinuation of alprazolam treatment in panic patients. *Am J Psychiatry* 1987; 144:303-308
6. Pecknold JC, Swinson RP, Kuch K, et al: Alprazolam in panic disorder and agoraphobia, results from a multicenter trial, III: discontinuation effects. *Arch Gen Psychiatry* 1988; 48:429-436
7. Miller LG, Greenblatt DJ, Barnhill JG, et al: Benzodiazepine receptor binding of triazolobenzodiazepines in vivo: increased receptor number with low-dose alprazolam. *J Neurochem* 1987; 49:1595-1601
8. Dunner DL, Ishiki D, Avery DH, et al: Effect of alprazolam and diazepam on anxiety and panic attacks in panic disorder: a controlled study. *J Clin Psychiatry* 1986; 47:458-460
9. von Korff MR, Eaton WW, Keyl PM: The epidemiology of panic attacks and panic disorder: results of three community studies. *Am J Epidemiol* 1985; 122:970-981
10. Cowley DS, Dager SR, Foster SI, et al: Clinical characteristics and response to sodium lactate of patients with infrequent panic attacks. *Am J Psychiatry* 1987; 144:795-798
11. Dager SR, Cowley DS, Dunner DL: Biological markers in panic states: lactate-induced panic and mitral valve prolapse. *Biol Psychiatry* 1987; 22:339-359
12. Hamilton M: The assessment of anxiety states by rating. *Br J Med Psychol* 1959; 32:50-55
13. Fontaine R, Chouinard G, Annable L: Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment. *Am J Psychiatry* 1984; 141:848-852
14. Vitaliano PP: Parametric statistical analysis of repeated measures experiments. *Psychoneuroendocrinology* 1982; 6:3-13
15. Rickels K, Case WG, Schweizer EG, et al: Low dose dependence in chronic benzodiazepine users: a preliminary report on 119 patients. *Psychopharmacol Bull* 1986; 22:407-415
16. Pecknold JC, McCluie DJ, Fleuri D, et al: Benzodiazepine withdrawal effects. *Prog Neuropsychopharmacol Biol Psychiatry* 1982; 6:517-522

Startle Modulation in Children With Posttraumatic Stress Disorder

Edward M. Ornitz, M.D., and Robert S. Pynoos, M.D., M.P.H.

Startle responses to bursts of white noise were recorded as blink reflexes 17–21 months after a traumatic event in six children with posttraumatic stress disorder (PTSD) and in six normal control children. A seventh child with PTSD was studied on four occasions during the 2 years following a stressful event. The startle responses were modulated by nonstartling acoustic prestimulation in order to study the inhibitory and facilitatory modulation of startle reaction by brainstem mechanisms. The children with PTSD experienced a significant loss of the normal inhibitory modulation of startle response, suggesting that the traumatic experience had induced a long-lasting brainstem dysfunction.

(Am J Psychiatry 1989; 146:866–870)

Posttraumatic stress disorder (PTSD) shows symptoms suggesting persistent hyperarousal, including insomnia, hypervigilance, autonomic hyperreactivity, and exaggerated startle responses (*DSM-III-R*). The sleep disorder (1–3) and the autonomic hyperreactivity (4–9) have been studied in the laboratory. Although abnormal startle response has been well documented in PTSD (5, 10–12), it has not been subjected to systematic neurophysiologic study. Biochemical studies and pharmacologic effects suggest central noradrenergic dysregulation in PTSD (13), and clonidine, which ameliorates hyperarousal in PTSD (14), decreases noradrenergic action and inhibits startle response (15).

Neurophysiologic studies of stress-induced alterations of startle reaction in the rat (16–18) may provide useful animal models of PTSD. In the laboratory, the startle response, a flexor motor response to a sud-

den stimulus (19, 20), is measured as whole body movement in the rat and as the magnitude of the reflex eye blink in human beings.

Startle modulation in the rat and in humans is mediated by polysynaptic brainstem mechanisms (21–23), with further modulation in humans by cortically mediated attention toward or away from eliciting stimuli (24–29).

Startle modulation by brainstem mechanisms can be induced in the rat and in humans if nonstartling stimuli precede the startling stimulus (30–35). Such warning stimuli can facilitate or inhibit response magnitude in subjects in nontask experiments without instruction, given certain temporal relationships between warning stimuli and startling stimuli (23, 34). Such effects are primarily brainstem mediated (15, 22, 36), and two classes of brainstem neurons have been associated with warning stimulus influence on startle reaction (30). One class of neurons is responsive to stimulus change when brief (20–200 msec) warning stimuli are presented within about 250 msec of startling stimuli; in mature subjects, that class of neurons inhibits the magnitude of startle response (35, 37). The other class of neurons is responsive to sustained stimulation (2000 msec or longer) and facilitates startle reaction (32). Since persistent exaggerated startle responses occur in PTSD, we anticipated that patients suffering from PTSD would show diminished startle inhibition in response to stimulus change at short warning intervals and augmented startle facilitation in response to sustained stimulation during longer warning intervals.

Recently, it has been demonstrated that PTSD occurs in children exposed to a life-threatening violent event (38). We present here a neurophysiologic study of startle modulation by prestimulation in a sample of such children who had been under fire during a sniper attack at their school playground that resulted in many injuries and two fatalities. In addition, we present the change in startle modulation in a single child over a period of 2 years following the murder of his father. These children's responses are compared to those of normal control subjects and to normative startle modulation data (39). We investigated startle modulation in children with PTSD and shall try to relate the findings to a neurophysiologic model derived from animal studies.

Received June 9, 1988; revision received Jan. 10, 1989; accepted Feb. 2, 1989. From the Department of Psychiatry and the Brain Research Institute, University of California, Los Angeles. Address reprint requests to Dr. Ornitz, A7-372, UCLA Neuropsychiatric Institute, 760 Westwood Plaza, Los Angeles, CA 90024.

Supported by grant HD-14193 from the National Institute of Child Health and Human Development, by the Alice and Julius Kantor Charitable Trust, and by the Bing Fund.

The authors thank Kathi Nader for coordinating subject recruitment and Andrea Kaplan and Mojdeh Sadeghpour for technical assistance.

Copyright © 1989 American Psychiatric Association.

METHOD

Six children, two boys and four girls between the ages of 8 and 13 years, in third to sixth grades at school, who had been under sniper fire on their school playground were studied on one occasion. Six normal control children from a different neighborhood, matched for age and sex, were also studied on one occasion. The traumatized children were studied 17–21 months after the event. Three had received direct fire and three had been pinned down on the playground. All six were preselected as meeting the *DSM-III* criteria for PTSD and as unequivocally exhibiting exaggerated posttrauma startle responses and hypervigilance. The diagnosis of PTSD required agreement in the data from three sources: self-report on the Child PTSD Reaction Index (38), parent report, and clinical assessment based on individual interviews. All subjects were in good health and not taking any medication.

An additional child with PTSD had witnessed his father's murder by a rifle shot. He exhibited excessive startle reactions in school (e.g., to the static noise of a microphone or to classmates yelling out answers). His posttrauma sleep disturbance was determined by polysomnography to be due to stage IV sleep phenomena (motor restlessness and terrified vocalizations). He was studied four times when he was between 7 and 9 years of age, from 6 weeks to 2 years after the traumatic event. He was receiving clonidine (to treat the sleep disturbance) before his last session.

Each child received an audiometric examination on the day of the test. One of the traumatized children had a 20-dB (SPL) hearing loss in one ear. A seventh traumatized child from the school sniper incident was not used because of >20-dB hearing loss in both ears. Written informed consent was obtained from all parents and children.

Warning stimuli (75-dB [SPL], 1000-Hz tones with 4-msec rise and fall times) and startle stimuli (104-dB [SPL], zero-rise-time, 50-msec bursts of white noise) were presented binaurally through TDH-49 circumaural earphones. The zero-rise-time brief bursts of white noise, rather than, for example, recordings of gun shots, were used as startling stimuli to facilitate comparison of the results with those obtained previously (39), to permit the use of normal children as control subjects, and because quantitative study of startle response and its modulation requires control over the rise time of the acoustic startling stimuli (19, 30, 31).

During each session, startling stimuli were presented 1) alone, 2) preceded by 25-msec warning stimuli 120 and 250 msec before the startling stimuli, and 3) preceded by sustained warning stimuli for 800 and 2000 msec before the startling stimuli. These five stimulus combinations were arranged in blocks of five trials each. Each type of trial occurred once in each ordinal position within the blocks. Each subject within each group started on the next successive block to balance order across subjects.

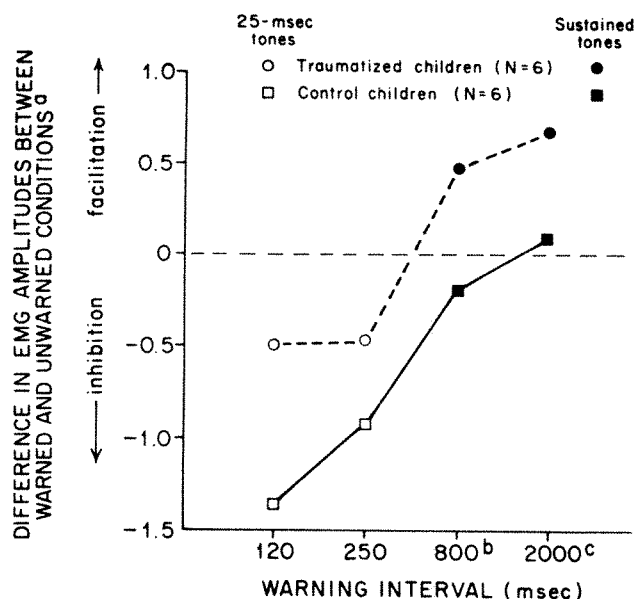
An orbicularis oculi electromyogram (EMG) was recorded from surface electrodes below the left lower eyelid margin. The EMG was AC-amplified (filters at half-amplitude 100–1000 Hz) and rectified and smoothed through a Coulbourn contour-following integrator (using a time constant of 700 msec). The output was digitized on a DEC 11/23 laboratory computer at a 500-Hz sampling rate. Peak amplitude within a 20–105-msec period after the startling stimulus was used to measure the startle response.

The subjects were familiarized with the laboratory and exposed to one sample warning stimulus and one startling stimulus. Then the electrodes were applied.

The subjects were given their choice of movies without sound and were instructed to watch the television set. They were told that the picture would be periodically turned off, at which time the warning stimulus, the startling stimulus, or both might be presented, and then the picture would come right back on. The television facilitated constant attention and arousal level throughout the experiment. The television picture was blanked out 2.5 seconds before trials in order to avoid interference with the auditory stimuli by a simultaneous conflicting visual stimulus. Visual and auditory monitoring of subjects through closed-circuit television and a room-to-room intercom complemented physiologic monitoring of tonic EMG activity, vertex EEG activity, heart rate, and eyelid position (by vertical direct-current electro-oculogram). These measures were made for a period of 2 minutes while ranges were established and then used to define a state of quiet alertness specific for each subject. Trials were presented according to a bounded random schedule of *minimal* intertrial intervals every 25–45 seconds. The computer withheld or aborted trials if the subject's state had changed so that the baseline physiologic measurements were outside the established range. Aborted trials were possible up to the time of startling stimulus onset and included two situations: 1) television picture off but *all* auditory stimuli withheld due to change in subject's state, then television back on; 2) television off, warning stimulus initiated but startling stimulus withheld due to unacceptable values within the final 200 msec before onset of the startling stimulus, then television back on. Intervals between completed trials were the sum of the minimal intertrial interval chosen by the computer and the additional time consumed waiting for the appropriate subject state. This method minimized the number of trials that could not be used because of artifact and ensured a relatively constant baseline physiologic state before stimulation. These procedures have been described in detail elsewhere (39).

All 12 subjects (the six children who had been on the playground and the six control children) completed three blocks (15 trials), and data analyses were based on these 180 trials. Only two trials (1.1%) had to be discarded (because lid or eye movements occurred during the 20 msec just after onset of the startling stimulus).

FIGURE 1. Modulation of Startle Amplitude by Prestimulation in Six Children With PTSD and in Six Control Children



^aResponse to startling stimulus presented after warning minus response to stimulus presented without warning. Values are log-transformed digital units.

^bSignificant difference between groups ($t=3.48$, $df=5$, $p=0.02$, two-tailed).

^cSignificant difference between groups ($t=2.60$, $df=5$, $p=0.05$, two-tailed).

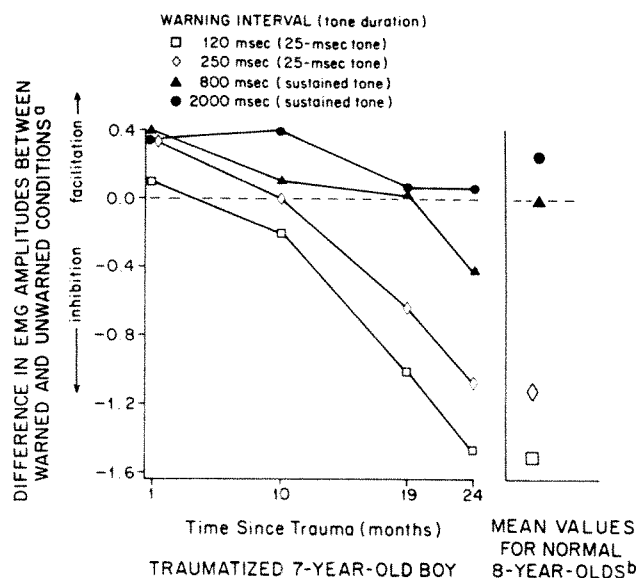
Amplitudes (log transformed) in each type of trial and the differences between warned and unwarned responses in the traumatized children and the control subjects were compared by means of paired t tests.

RESULTS

The startle responses of the traumatized children were smaller than those of the control children in all five types of trials. For the unwarned trials, this difference was statistically significant ($t=2.97$, $df=5$, $p=0.03$, two-tailed). In the traumatized children, the startle response was too small to measure on 11 of 90 trials, while only three of 90 trials were too small to measure in the control subjects. On the television monitor, four of the six traumatized children were visually observed to have barely perceptible blink responses to the startling stimuli, and the amplitudes of the EMG-derived responses were proportionally small. None of the control children had unusually small responses.

Amplitude modulation was evaluated by subtracting the log-transformed values of the responses to the unwarned startling stimuli from the values of the responses to the warned startling stimuli for each subject (figure 1). The startle response modulation for the 8–13-year-old children in the control group was almost identical to that reported for larger groups of normal

FIGURE 2. Changes in Startle Amplitude Modulation During a 2-Year Period Following Trauma in a 7-Year-Old Boy and Values for Normal 8-Year-Olds



^aResponse to startling stimulus presented after warning minus response to stimulus presented without warning.

^bValues are log-transformed digital units reported by Ornitz et al. (39).

8-year-olds and adults (39). In contrast, the traumatized children showed less startle response inhibition in response to prestimulation at 120- and 250-msec warning intervals and more startle response facilitation in response to sustained prestimulation for 800 and 2000 msec. The group differences were statistically significant for the responses to the two sustained prestimulations.

The child who had witnessed his father's murder was studied at ages 7 years 1 month, 7 years 10 months, 8 years 7 months, and 9 years 0 months. The amplitude of his response to the unwarned startling stimuli was greater than the mean amplitude of the other children with PTSD and similar to that of the control children on each occasion. Compared to normal 8-year-old boys (39), he showed normal values for startle amplitude modulation in response to 2000-msec sustained tones during each of the four sessions, a slight increase in facilitation in response to the 800-msec sustained tones during the first session, and marked loss of inhibition in response to the two short warning intervals during the first and second sessions (figure 2). Across the four sessions there was a progressive shift in amplitude modulation in the direction of increasing startle response inhibition. Between 19 and 24 months after the trauma, all of this child's responses approximated normal values for startle modulation. Interpretation of the results at 24 months after the trauma is complicated, since the child was taking clonidine, a potent startle inhibitor (15).

DISCUSSION

The "symptoms of release" (4) in PTSD, including the startle reaction, have been described in terms of a "conditioned emotional response" (4, 11, 40) in which the sights and sounds of the traumatic event serve as conditioning stimuli that potentiate the innate startle response. Activation of the conditioned startle response is said to require meaningful visual and auditory stimuli that simulate the actual stimuli of, for example, combat (11). The startling stimuli used in this study were not designed to simulate the sounds of gunshots; rather, these sudden short bursts of white noise are described by most children as a loud hiss. Hence, the relative loss of prestimulation-induced inhibitory startle modulation should be due to different, but perhaps related, neural mechanisms from those which underlie the conditioned emotional responses of PTSD.

A reasonable animal model for the conditioned emotional response concept of startle pathology in PTSD is the fear-potentiated startle paradigm (16, 17). The amplitude of the rat startle response to sudden loud sounds is augmented in the presence of light that has previously been paired with painful shocks (41). The light itself does not elicit a startle reaction, and the sounds have not been paired with the shocks. Potentiated startle reaction occurs when the startle responses to the sounds are greater in the presence of the light (the conditioned stimulus) than in the dark. The primary acoustic startle circuit in the brainstem (ear to ventral cochlear nucleus to ventral nucleus of lateral lemniscus to nucleus reticularis pontis caudalis to effector muscles) (21) is modulated by more rostral brainstem pathways, which mediate fear-conditioned enhancement of acoustic startle reactions (17). These pathways convey the effect of the fear-associated light to the superior colliculus, which projects to the ventral nucleus of lateral lemniscus, conveying the effect of fear conditioning to the direct startle pathway (42-44).

A plausible animal model for the relative loss of prestimulation-induced inhibitory startle modulation in the children with PTSD is the loss of startle inhibition induced by a cold-swim stress test in rats. After a forced swim in 2-°C water before exposure to acoustic startling stimuli alone and startling stimuli preceded at 100 msec by nonstartling sounds, the expected prestimulation-induced startle inhibition was impaired by preexposure to this stress (18). A pathway mediating startle inhibition projects from the inferior colliculus (36) and the lateral tegmental area (22) onto the primary acoustic startle pathway at the nucleus reticularis pontis caudalis (22), one synapse away from the ventral nucleus of lateral lemniscus, where the projections from the fear-potentiated startle modulation circuitry impinge on the primary pathway (16, 17).

Thus, the circuitry mediating the conditioned potentiation of startle response and the inhibition of startle response impinge on the direct startle pathway at closely related points. Hence, impairment of startle inhibition, resulting from previous stress, may reflect a

dysfunction of startle modulation that is linked neurophysiologically to the conditioned fear potentiation of the startle reaction.

The same experimental stress that induced impairment of startle inhibition induces analgesia (18). Thus, stress may induce reduced as well as increased response to environmental stimulation. The small startle responses to the unwarned startling stimuli (which did not simulate the specific sounds of the traumatic event) found in four of the children with PTSD suggest reduced responsiveness. The "cognitive and behavioral shutting down" described in PTSD (13) may be related to these observations and may reflect cortically mediated attentional dysfunction. Attentional shifts exert downstream control over brainstem-mediated startle responses (45).

Impaired startle inhibition in the children with PTSD did not depend on the conditioned emotional component of the "symptoms of release" (4), i.e., replication of the actual traumatic stimuli. Rather, it may reflect an underlying long-lasting alteration in the brainstem circuits subserving startle modulation. The children with PTSD showed impaired prestimulation inhibition of startle response 17-21 months after the traumatic event.

Inhibitory startle modulation is a developmentally acquired function that matures when a child is about 8 years of age (39). The loss of inhibitory startle modulation in the children with PTSD could represent a regression from mature levels of prestimulation-induced inhibition to those observed in normal preschool children (39). The average values obtained for the control subjects in this study are almost identical to those obtained for normal 8-year-old children and young adults, while the values for the children with PTSD are almost identical to those reported for normal 5-year-old children. Thus, inhibitory startle modulation is an acquired brainstem-mediated function that can be reversed by severe stress. The progressively changing values for the child who witnessed his father's murder suggest that the loss of inhibitory modulation may be most severe soon after the stress and may be ameliorated with the passage of time and, possibly, by the influence of clonidine, an inhibitor of startle response experimentally in the rat (15) and clinically in patients with PTSD (14).

This was the first study of experimental startle modulation in PTSD. It had limitations that should be redressed in future studies. The sample size was small, and it was not possible to match the control and traumatized children for ethnicity and socioeconomic status, although they were matched for age and sex.

If these preliminary results can be replicated in larger samples, examination of startle modulation may prove to be useful in the assessment of children after trauma. It may provide a procedure to test the efficacy of medications in treating arousal behavior associated with PTSD. Future studies may clarify the relationship between startle reactions and hypervigilant behavior

by testing for the relative influence of cortical mediation and brainstem mechanisms.

REFERENCES

1. Hefez A, Metz L, Lavie P: Long-term effects of extreme situational stress on sleep and dreaming. *Am J Psychiatry* 1987; 144:344-347
2. Kramer M, Schoen LS, Kinney L: The dream experience in dream-disturbed Vietnam veterans, in *Post-Traumatic Stress Disorder: Psychological and Biological Sequelae*. Edited by van der Kolk BA. Washington, DC, American Psychiatric Press, 1984
3. Lavie P, Hefez A, Halperin G, et al: Long-term effects of traumatic war-related events on sleep. *Am J Psychiatry* 1979; 136: 175-178
4. Kolb LC: A neuropsychological hypothesis explaining posttraumatic stress disorders. *Am J Psychiatry* 1987; 144:989-995
5. Pitman R, Orr S, Forgue D, et al: Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. *Arch Gen Psychiatry* 1987; 44:970-975
6. Blanchard E, Kolb L, Gerardi R, et al: Cardiac response to relevant stimuli as an adjunctive tool for diagnosing post-traumatic stress disorder in Vietnam veterans. *Behavior Therapy* 1986; 17:592-606
7. Malloy P, Fairbank J, Keane T: Validation of a multimethod assessment of posttraumatic stress disorders in Vietnam veterans. *J Consult Clin Psychol* 1983; 51:488-494
8. Blanchard E, Kolb L, Pallmeyer T, et al: A psychophysiological study of post traumatic stress disorder in Vietnam veterans. *Psychiatr Q* 1982; 54:220-229
9. Brende J: Electrodermal responses in post-traumatic syndromes: a pilot study of cerebral hemisphere functioning in Vietnam veterans. *J Nerv Ment Dis* 1982; 170:352-361
10. Kardiner A, Spiegel H: *The Traumatic Neuroses of War*. New York, Paul Hoeber, 1947
11. Kolb L: The post-traumatic stress disorders of combat: a subgroup with a conditioned emotional response. *Milit Med* 1984; 149:237-243
12. Lerer B, Bleich A, Kotler M, et al: Posttraumatic stress disorder in Israeli combat veterans. *Arch Gen Psychiatry* 1987; 44:976-981
13. Krystal J, Kosten T, Perry B, et al: Neurobiological aspects of PTSD: review of clinical and preclinical studies. *Behavioral Therapy* 1989; 20:177-198
14. Kolb LC, Burris BC, Griffiths S: Propranolol and clonidine in treatment of the chronic post-traumatic stress disorders of war, in *Post-Traumatic Stress Disorder: Psychological and Biological Sequelae*. Edited by van der Kolk BA. Washington, DC, American Psychiatric Press, 1984
15. Davis M: The mammalian startle response, in *Neural Mechanisms of Startle Behavior*. Edited by Eaton R. New York, Plenum, 1984
16. Davis M: Neurobiologic perspectives on anxiety. *Psychopharmacol Bull* 1983; 19:457-465
17. Davis M: Pharmacological and anatomical analysis of fear conditioning using the fear-potentiated startle paradigm. *Behav Neurosci* 1986; 100:814-824
18. Leitner D: Alterations in other sensory modalities accompanying stress analgesia as measured by startle reflex modification. *Ann NY Acad Sci* 1986; 467:82-92
19. Graham F: Distinguishing among orienting, defense, and startle reflexes, in *The Orienting Reflex in Humans: An International Conference Sponsored by the Scientific Affairs Division of the North Atlantic Treaty Organization*. Edited by Kimmel H, van Olst E, Orlebeke J. Hillsdale, NJ, Lawrence Erlbaum Associates, 1979
20. Wilkins D, Hallett M, Wess M: Audiogenic startle reflex of man and its relationship to startle syndromes. *Brain* 1986; 109:561-573
21. Davis M, Gendelman D, Tischler M, et al: A primary acoustic startle circuit: lesion and stimulation studies. *J Neurosci* 1982; 2:791-805
22. Leitner D, Powers A, Stitt C, et al: Midbrain reticular formation involvement in the inhibition of acoustic startle. *Physiol Behav* 1981; 26:259-268
23. Hoffman H, Ison J: Reflex modification in the domain of startle, I: some empirical findings and their implications for how the nervous system processes sensory input. *Psychol Rev* 1980; 87: 175-189
24. Anthony B, Graham F: Evidence for sensory-selective set in young infants. *Science* 1983; 220:742-744
25. Hackley S, Graham F: Early selective attention effects on cutaneous and acoustic blink reflexes. *Physiological Psychol* 1984; 11:235-242
26. Silverstein L, Graham F, Bohlin G: Selective attention effects on the reflex blink. *Psychophysiology* 1981; 18:240-247
27. Simons R, Zelson M: Engaging visual stimuli and reflex blink modification. *Psychophysiology* 1985; 22:44-49
28. Del Pezzo E, Hoffman H: Attentional factors in the inhibition of a reflex by a visual stimulus. *Science* 1980; 210:673-674
29. Bohlin G, Graham F, Silverstein L, et al: Cardiac orienting and startle blink modification in novel and signal situations. *Psychophysiology* 1981; 18:603-611
30. Graham F, Strock B, Zeigler B: Excitatory and inhibitory influences on reflex responsiveness, in *Minnesota Symposium on Child Psychology*. Edited by Collins W. Hillsdale, NJ, Lawrence Erlbaum Associates, 1981
31. Graham F: The more or less startling effects of weak prestimulation. *Psychophysiology* 1975; 12:238-248
32. Graham F, Putnam L, Leavitt L: Lead-stimulation effects on human cardiac orienting and blink reflexes. *J Exp Psychol [Hum Percept]* 1975; 104:161-169
33. Ison J, Ashkenazi B: Effects of a warning stimulus on reflex elicitation and inhibition. *Psychophysiology* 1980; 17:586-591
34. Hoffman H, Cohen M, Stitt C: Acoustic augmentation and inhibition of the human eyeblink. *J Exp Psychol [Hum Percept]* 1981; 7:1357-1362
35. Graham F, Murray G: Discordant effects of weak prestimulation on magnitude and latency of the reflex blink. *Physiological Psychol* 1977; 5:108-114
36. Leitner D, Cohen M: Role of the inferior colliculus in the inhibition of acoustic startle in the rat. *Physiol Behav* 1985; 34: 65-70
37. Harbin T, Berg W: The effects of age and prestimulus duration upon reflex inhibition. *Psychophysiology* 1983; 20:603-610
38. Pynoos R, Frederick C, Nader K, et al: Life threat and post-traumatic stress in school-age children. *Arch Gen Psychiatry* 1987; 44:1057-1063
39. Ornitz E, Guthrie D, Kaplan A, et al: Maturation of startle modulation. *Psychophysiology* 1986; 23:624-634
40. Kolb L, Motalipassi: The conditioned emotional response: a sub-class of the chronic and delayed post-traumatic stress disorder. *Psychiatr Annals* 1982; 12:979-987
41. Brown J, Kalish I, Farber I: Conditioned fear as revealed by magnitude of startle response to an auditory stimulus. *J Experimental Physiology* 1951; 41:317-327
42. Tischler M, Davis M: A visual pathway that mediates fear-conditioned enhancement of acoustic startle. *Brain Res* 1983; 276:55-71
43. Hitchcock J, Davis M: Lesions of the amygdala, but not of the cerebellum or red nucleus, block conditioned fear as measured with the potentiated startle paradigm. *Behav Neurosci* 1986; 100:11-22
44. Hitchcock J, Davis M: Fear-potentiated startle using an auditory conditioned stimulus: effect of lesions of the amygdala. *Physiol Behav* 1987; 39:403-408
45. Anthony B: In the blink of an eye: implications of reflex modification for information processing. *Advances in Psychophysiology* 1985; 1:167-218

Developmental Perspectives in Child and Adolescent Depressive Symptoms in a Community Sample

Javad H. Kashani, M.D., Tomas K. Rosenberg, M.A., and John C. Reid, Ph.D.

This developmental study provides some normative data on the distribution of depressive symptoms in 210 children and adolescents in three different age groups (8, 12, and 17 years) from a nonclinically referred sample. The Child Assessment Schedule and other instruments were used. Studying depression from a dimensional point of view, the authors found withdrawal, pessimism, horrible dreams, and suicidal ideation and tendency in the different age groups to be closely related to depressive symptoms.

(Am J Psychiatry 1989; 146:871-875)

In the last 10 years significant advancements have been made in the understanding of several aspects of childhood depression, including epidemiology, phenomenology, and biology, as well as treatment (1-7). Study of the developmental aspects of child and adolescent depression, however, has lagged far behind. Recent books by Rutter et al. (8) and Trad (9) were largely devoted to developmental issues of depression in young people, but few empirical studies have been done. Rutter (10) emphasized the pressing need for additional empirical studies concerning the developmental aspects of childhood depression by stating, "Perhaps the most basic need in the study of childhood depression is to determine how the manifestations of depression vary with age . . ." Digdon and Gotlib's review (11) recommended investigation of the frequency of "depressive" behavior in nondepressed children. Normative data are essential to determine whether some behaviors are sufficiently rare to qualify as symptoms of depression, since the prevalence of many normative behaviors varies with age. Further, in supporting a developmental approach to child and adolescent depression, Garber (12) stated that developmental perspectives do not dictate that the symptom-complex diagnosis be abandoned, but, rather, that it

should be complemented by the addition of phase-specific manifestations to, and deletion of age-inappropriate symptoms from, the syndrome.

Ryan et al. (13), who studied clinically referred children and adolescents, recommended that symptoms such as somatic complaints, social withdrawal, and hopelessness, which are commonly recognized as depressive but are absent from DSM-III criteria, be considered for inclusion in the diagnostic criteria for this age group.

Despite the recommendations of these investigators and others (14-17), empirical data on developmental changes in childhood and adolescent depression are rare (12, 13, 18). The purposes of this study, therefore, were 1) to describe depressive symptoms in three different age groups (8-, 12-, and 17-year-olds) from a general population and 2) to ascertain which depressive items were most closely related to a quantitative measure of depression.

METHOD

Subjects

A systematic sample of 210 children and adolescents was drawn from public school lists of 4,810 subjects (there were 1,745 8-year-olds, 1,578 12-year-olds, and 1,487 17-year-olds). Children were stratified by each of the three age groups and by sex, and then every nth name was drawn. Twenty percent of the families were in socioeconomic class I (19), 34.8% in class II, 27.1% in class III, 16.7% in class IV, and 1.4% in class V. Eighty-nine percent of the subjects were Caucasian, 9% were black, and 2% were Oriental/other.

Procedure

Three hundred seventy-seven families were telephoned. After the experimenters explained the procedure and incentive for participation (\$50.00 per child), 289 (77%) agreed to participate; we sequentially proceeded in using those who had agreed to participate, but we stopped when the predetermined age and gender sample limits were reached. Students not attending public school and families with no telephones were not included. The interview, conducted by doctoral stu-

Received Jan. 8, 1988; revision received July 13, 1988; accepted Dec. 29, 1988. From the University of Missouri-Columbia and Mid-Missouri Mental Health Center, Columbia. Address reprint requests to Dr. Kashani, Department of Psychiatry, University of Missouri-Columbia, 3 Hospital Dr., Columbia, MO 65201.

The authors thank Gabrielle A. Carlson, M.D., and Judy Garber, Ph.D., for their comments about the manuscript.

Copyright © 1989 American Psychiatric Association.

dents in psychology or child and family development, took place in the subject's home and involved both the child and a parent, usually the mother. Both parents (if available) and the children and adolescents signed a consent form. The interview format consisted of the administration of the Child Assessment Schedule, the parental version of the Child Assessment Schedule, and other instruments noted below. Interviewers were trained in administering the Child Assessment Schedule until two criteria were met: achievement of an item-by-item reliability (kappa) of 0.80 during practice interview role playing and achievement of an interrater reliability (kappa) of 0.85. To maintain quality control and to prevent interviewer drift, ongoing supervision and retraining sessions were periodically carried out.

Assessments

The Child Assessment Schedule is a semistructured diagnostic interview. A parallel form of the instrument is administered to the parent. The two instruments determine whether *DSM-III* criteria are met for the following diagnoses: attention deficit disorder, conduct disorder, separation anxiety disorder, overanxious disorder, schizoid disorder, oppositional disorder, major depression, dysthymic disorder, obsessive-compulsive disorder, phobic disorders, enuresis, and encopresis. The two instruments provide for examination of problems in broad content areas such as friendship and school. In addition, their symptom complex scales measure the number of symptoms relevant to a specific diagnosis. The reliability and validity of the Child Assessment Schedule have been previously reported by Hodges et al. (20–22).

The Birleson Depression Self-Rating Scale for Children is an 18-item self-report scale measuring depression. There is some evidence that both the reliability and content validity are satisfactory (23, 24).

The Hopelessness Scale for Children, developed by Kazdin et al., contains 17 dichotomous items assessing negative expectancies about the future. The internal consistency (alpha) of this instrument has ranged from 0.75 to 0.97 (25, 26).

The Revised Children's Manifest Anxiety Scale is a 15-item self-report scale that assesses child and adolescent anxiety. It has the following three subscales: worry/oversensitivity, concentration, and physiologic. A greater anxiety in individuals is reflected by a higher score on subscales. Reynolds and Richmond (27, 28) have reported the psychometric properties of this scale.

Statistical Analyses

The Birleson, hopelessness, and children's anxiety scales are all continuous scales, and this study did not use a standard cutoff point. Differences in item frequencies between the age and diagnostic groups were analyzed by chi-square tests, which were also partitioned (29). Overall differences among age groups for the continuous scales were assessed by Kruskal-Wallis

tests. Significant overall differences were followed up with post hoc pairwise comparisons of group medians (30). Tests were two-tailed. Stepwise multiple regression determined the relative importance of the various hopelessness and Birleson items to the Child Assessment Schedule's depression symptom complex score. This regression technique lets us identify a group of hopelessness and Birleson items that are related to the symptom complex score.

Since we ran several statistical tests, the type I error rate could be high. This may be compensated for by the conservative Bonferroni technique. For the item frequencies, there were 74 Child Assessment Schedule, Birleson, and hopelessness items yielding a Bonferroni adjusted criterion of $p < 0.0007$. For the scale scores, there were 17 child assessment, Birleson, hopelessness, and children's anxiety scales giving a Bonferroni adjusted criterion of $p < 0.003$. However, for this exploratory study we felt it more appropriate to report the actual p values obtained.

RESULTS

Symptom Frequencies

The first purpose of the study was to describe depressive symptoms in the three age groups. Reports of the following child assessment items became more frequent with increasing age: being more tired than before, not caring whether they hurt themselves, agitation when sad, and frequent irritability (table 1). Of all the depression-related items, only the item about crying decreased with age, with 12- and 17-year-olds combined ($\chi^2 = 8.08$, $df = 1$, $p = 0.004$).

Reports of the following Birleson items became more frequent with the older children: not liking to go out and play, not having lots of energy, and feeling very bored. Reports of four Birleson items became less frequent with increasing age: not looking forward to things as much as they used to, having stomachaches, not sticking up for themselves, and having horrible dreams.

Reports of one hopelessness scale item, tomorrow being unclear and confusing, became more frequent with increasing age. Reports of two hopelessness scale items became less frequent with increasing age: not getting more of the good things out of life than others and no use trying to get what I want because I won't get it.

Scale Score Differences

There were no significant differences among the three age groups on the hopelessness score, the Birleson score, or the children's anxiety scale's worry/oversensitivity subscale or concentration subscale. The depression symptom complex score increased as age increased ($\chi^2 = 9.36$, $df = 2$, $p = 0.009$, Kruskal-Wallis

TABLE 1. Frequency of Depression-Related Items From Three Scales Among Three Age Groups of Children and Adolescents From the General Population

Scale and Item	8-Year-Olds (N=70)		12-Year-Olds (N=70)		17-Year-Olds (N=70)		χ^2 (df=2)	p
	N	%	N	%	N	%		
Child Assessment Schedule								
More tired than before	16	22.9	11	15.7	24	34.3	6.68	0.04
Doesn't care whether hurts self ^a	4	5.7	11	15.7	26	37.1	22.97	0.001
Agitation or hyperactivity when sad ^a	10	14.3	15	21.4	24	34.3	8.04	0.02
Irritable a lot ^a	13	18.6	15	21.4	30	42.9	12.34	0.002
Birleson scale ^b								
Not looking forward to things as much as used to ^a	38	54.3	33	47.1	22	31.4	7.76	0.02
Not liking to go out and play ^a	12	17.1	17	24.3	34	48.6	18.09	0.001
Having stomachaches ^a	57	81.4	39	55.7	29	41.4	23.88	0.001
Not having lots of energy ^a	26	37.1	29	41.4	47	67.1	14.75	0.001
Not sticking up for self ^c	32	45.7	14	20.0	18	25.7	12.05	0.002
Having horrible dreams ^{a,c}	38	54.3	19	27.1	17	24.3	16.82	0.001
Feeling very bored ^c	49	70.0	65	92.9	59	84.3	12.86	0.002
Hopelessness Scale for Children ^b								
Thinking I won't get more of the good things out of life than others ^a	44	62.9	38	54.3	24	34.3	12.04	0.002
Thinking tomorrow is unclear and confusing ^a	11	15.7	9	12.9	24	34.3	11.44	0.003
Thinking there is no use trying to get what I want because I won't get it ^a	13	18.6	7	10.0	2	2.9	9.24	0.01

^aSignificant difference between the 8- and the 12-year-olds (df=1, $p<0.05$).

^bThe response frequencies reflect the negative aspect of the questions.

^cSignificant difference between the 8- and 12-year-olds combined and the 17-year-olds (df=1, $p<0.05$).

test) with means \pm SD of 4.71 ± 3.94 for the 8-year-olds and 4.93 ± 3.91 for the 12-year-olds. These means differed from that for the 17-year-olds (6.23 ± 3.71) but not from each other. The scores on the children's anxiety scale's physiological subscale decreased as age increased ($\chi^2=14.83$, df=2, $p=0.0006$), with the mean scores of the 12-year-olds (2.83 ± 2.17) and 17-year-olds (2.86 ± 2.23) differing from that of the 8-year-olds (4.01 ± 2.10) but not from each other.

Relative Relevance of Hopelessness and Birleson Items

The second purpose of the study was to determine which depressive items from the hopelessness and the Birleson scales were related to the children's anxiety symptom complex depression score. Since only six children—one 8-year-old, one 12-year-old, and four 17-year-olds—met all *DSM-III* criteria for depression, we used the children's anxiety symptom complex depression score as the dependent variable. The mean \pm SD symptom complex depression score for the six depressed children was 11.8 ± 3.43 versus 5.1 ± 3.74 for the 204 remaining children ($\chi^2=11.94$, df=1, $p=0.0003$). The independent variables were the item scores treated as dummy variables. Presumably the aspects addressed by the items in this subset are the most relevant to the depression symptom complex score. Thus, the subset identified can be thought of as indicating which aspects of behavior related to depression are the most closely linked at various ages. A separate

stepwise regression analysis was performed for each age group (table 2).

Five of the 35 items from the hopelessness and the Birleson scales explained 44% of the variance in the depression symptom complex score for the 8-year-old group (see table 2). Five different items from the hopelessness and the Birleson scales explained 46% of the variance in the depression symptom complex score for the 12-year-olds. Two items from the hopelessness and Birleson scales accounted for 30% of the variance in the depression symptom complex score for the 17-year-olds.

DISCUSSION

This study provides data on the distribution of depressive symptoms in three different age groups from a community sample and represents a preliminary step for developmental studies in depression. The data comparing the three age groups indicated that older children cry less often, are more likely to view the occurrence of bad things as being their fault, and are more likely to be careless about their safety. While it is conceivable that these are independent and unrelated symptoms, an alternative interpretation is possible. That is, older children who interpret the occurrence of bad things as being their fault may blame themselves for the event. In turn, this self-blame or critical attitude toward self may lead to a self-punitive attitude as the child approaches adolescence. The child's increased

TABLE 2. Regression Analyses of Items on the Birleson and Hopelessness Scales for Three Age Groups of Children and Adolescents From the General Population^a

Age Group and Scale Item	Model R ²	F	df	p
8-year-olds (N=70)				
Thinking I never get what I want so it is dumb to want anything ^b	0.15	12.04	1, 68	0.0009
Not liking to go out and play ^c	0.26	10.13	2, 67	0.002
Not liking to talk with family ^c	0.36	9.87	3, 66	0.003
Not having enough time to finish things ^b	0.40	4.60	4, 65	0.04
Not thinking I will have more good than bad times ^b	0.44	4.41	5, 64	0.04
12-year-olds (N=70)				
Not sleeping very well ^c	0.17	14.24	1, 68	0.0003
Not thinking I will be happier when I grow up ^b	0.30	12.11	2, 67	0.0009
Thinking things will not work out the way I want ^b	0.37	7.57	3, 66	0.008
Not enjoying food ^c	0.42	5.52	4, 65	0.02
Having stomachaches ^c	0.46	4.86	5, 64	0.03
17-year-olds (N=70)				
Having horrible dreams ^c	0.22	19.46	1, 68	0.0001
Thinking life is not worth living ^c	0.30	7.35	2, 67	0.009

^aThe dependent variable is the Child Assessment Schedule symptom complex depression score. No other variables reached the $p < 0.05$ criterion for inclusion in the equation.

^bHopelessness Scale for Children.

^cBirleson scale.

carelessness about his or her safety may be a manifestation of a self-punitive attitude. Therefore, the results showing increased carelessness in older children provide some support for this possible association. However, specific testing of this hypothesized link between self-blame and a self-punitive attitude is necessary.

When the different age groups' hopelessness and overall scale scores were compared, we did not see any significant differences among the age groups. This may indicate that the overall hopelessness scores of children in a community sample may not increase as the children become older. Although this result is in agreement with the findings of Garber (12) and Carlson and Cantwell (31), it does not support the hypothesis (12) that increasing cognitive functioning is positively correlated with a hopelessness score. This hypothesis holds that as a person matures and cognitive functioning increases, the person is more capable of grasping the concept of hopelessness. The absence of an association between increasing age and increasing hopelessness score in our study may be due to disparate rates of development for cognitive functioning and for grasping the concept of hopelessness. Alternatively, the proposed link between cognitive functioning and hope-

lessness may not exist. Clarification of this issue awaits further theoretical explication of the hopelessness mechanism and empirical testing of a revised model.

The overall Birleson scale score also did not differ across the different age groups. Similar results were reported by Birleson et al. (24), who found no age differences in Birleson scale scores between prepuberty and early adolescence (14 years). A possible explanation may be a lack of sensitivity by the Birleson scale toward the adolescent group; alternatively, this lack of difference may result from the inclusion on the Birleson scale of some non-*DSM-III* depression items (e.g., I can stick up for myself). Thus, even though the frequency of reports of *DSM-III* depression items may increase with age, frequency of reports of the associated non-*DSM-III* items on the scale may not change as a function of age. Support for the idea that there will be an increase in depression with age is shown by the result that the overall depressive symptoms, as measured by the Child Assessment Schedule items derived from the *DSM-III* criteria, did increase with age. Birleson et al. concluded that this rating scale would be better suited for use in research that compared clinically depressed individuals with nondepressed groups. Therefore, when there is a low prevalence of depressive symptoms, the ability to discriminate the different age groups is not high.

Viewing depression from a categorical point of view, we found that the 8- and 12-year-olds were similar in terms of distribution of a *DSM-III* depressive disorder (1.4% prevalence in both age groups), but the condition was four times more common in late adolescence (5.7% prevalence for the 17-year-olds). This supports previous findings (32) that depression does increase with age from childhood to adolescence.

The results of the regression analyses indicated that more depressive symptoms in the 8-year-old group were associated with more withdrawal (not liking to play, not liking to talk with family) and pessimism (never getting what they want, thinking that they will not have a good time). More depressive symptoms in the 12-year-old group were associated with pessimism about the future (won't be happier when they grow up, things will not work out), as well as physical symptoms (not sleeping well, not having a good appetite, and stomachaches). The 17-year-old group's depressive symptoms were related to having horrible dreams and suicidal ideation.

The withdrawal exhibited by the 8-year-olds with depressive symptoms may eventuate in delayed development of their social skills and a social support network. Assuming that withdrawal will be associated with social isolation due to the reciprocal nature of social interaction, the social isolation may itself perpetuate the dysfunction by affecting either the person directly or the resources available to the individual. If this is true, intervention to ameliorate the effects of the withdrawal may be clinically warranted.

The pessimistic attitude expressed by the 8- and 12-year-olds may lead to psychiatric disorders during

adolescence and in later years. This assumes an association between pessimism and psychopathology. Support for this comes from a recent study (33) which found that "caseness" (i.e., having a psychiatric disorder, being dysfunctional, and needing treatment) was more often diagnosed in adolescents with a pessimistic attitude than in a control group. Whether pessimism is a precursor to psychopathology, a coexisting symptom, or perhaps a result of psychopathology awaits future research.

REFERENCES

1. Puig-Antich J, Lukens E, Davies M, et al: Psychosocial functioning in prepubertal major depressive disorders, II: interpersonal relationships after sustained recovery from affective episode. *Arch Gen Psychiatry* 1985; 42:511-517
2. Poznanski E, Mokros HB, Grossman J, et al: Diagnostic criteria in childhood depression. *Am J Psychiatry* 1985; 142:1168-1173
3. Petti TA: Behavioral approaches in the treatment of depressed children, in *Affective Disorders in Children and Adolescents*. Edited by Cantwell DP, Carlson GA. Jamaica, NY, Spectrum, 1983
4. Cantwell DP: Childhood depression, in *Advances in Clinical Child Psychology*, vol 5. Edited by Lahey BB, Kazdin AE. New York, Plenum, 1982
5. Cytryn L, McKnew DH Jr, Bunney WE Jr: Diagnosis of depression in children: a reassessment. *Am J Psychiatry* 1980; 137: 22-25
6. Beardslee WR, Bemporad J, Keller MB, et al: Children of parents with major affective disorder: a review. *Am J Psychiatry* 1983; 140:825-832
7. Weller WB, Weller RA, Preskorn SH, et al: Steady-state plasma imipramine levels in prepubertal depressed children. *Am J Psychiatry* 1982; 139:506-508
8. Rutter M, Izard CE, Read BR (eds): *Depression in Young People—Developmental and Clinical Perspectives*. New York, Guilford Press, 1986
9. Trad PV: *Infant and Childhood Depression: Developmental Factors*. New York, John Wiley & Sons, 1987
10. Rutter M: Child psychiatry: the interface between clinical and developmental research. *Psychol Med* 1986; 16:151-169
11. Digdon N, Gotlib IH: Developmental considerations in the study of childhood depression, in *Annual Progress in Child Psychiatry and Child Development*. Edited by Chess S, Thomas A. New York, Brunner/Mazel, 1986
12. Garber J: The developmental progression of depression in female children, in *Childhood Depression*. Edited by Cicchetti D, Schneider-Rosen K. San Francisco, Jossey-Bass, 1984
13. Ryan ND, Puig-Antich J, Ambrosini P, et al: The clinical picture of major depression in children and adolescents. *Arch Gen Psychiatry* 1987; 44:854-861
14. Malmquist CP: Depressions in childhood and adolescence, 1. *N Engl J Med* 1971; 284:887-893
15. Bemporad JR: Childhood depression from a developmental perspective, in *Psychiatry 1982: The American Psychiatric Association Annual Review*. Edited by Grinspoon L. Washington, DC, American Psychiatric Press, 1982
16. Philips I, Friedlander S: Conceptual problems in the study of depression in childhood. *Ibid*
17. Herzog DB, Rathbun JM: Childhood depression: developmental considerations. *Am J Dis Child* 1982; 136:115-120
18. McConville BF, Boag LC, Purohit AP: Three types of childhood depression. *Can Psychiatr Assoc J* 1973; 18:133-138
19. Hollingshead AB, Redlich FC: *Social Class and Mental Illness*. New York, John Wiley & Sons, 1958
20. Hodges KK, Kline J, Fitch P, et al: The Child Assessment Schedule: a diagnostic interview for research and clinical use. *Catalog of Selected Documents in Psychology* 1981; 11:56
21. Hodges K, McKnew D, Cytryn L, et al: The Child Assessment Schedule (CAS) Diagnostic Interview: a report on reliability and validity. *J Am Acad Child Psychiatry* 1982; 21:468-473
22. Hodges K, McKnew D, Burbach DJ, et al: Diagnostic concordance between the Child Assessment Schedule (CAS) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-P) in an outpatient sample using lay interviews. *J Am Acad Child Adolesc Psychiatry* 1987; 26:654-661
23. Birlleson P: The validity of depressive disorder in childhood and the development of a self-rating scale: a research report. *J Child Psychol Psychiatry* 1981; 22:73-88
24. Birlleson P, Hudson I, Buchanan DF, et al: Clinical evaluation of a self-rating scale for depressive disorder in childhood (Depression Self-Rating Scale). *J Child Psychol Psychiatry* 1987; 28:43-60
25. Kazdin AE, French NH, Unis AS, et al: Hopelessness, depression, and suicidal intent among psychiatrically disturbed inpatient children. *J Consult Clin Psychol* 1983; 51:504-510
26. Kazdin AE, Rodgers A, Colbus D: The Hopelessness Scale for Children: psychometric characteristics and concurrent validity. *J Consult Clin Psychol* 1986; 54:241-245
27. Reynolds CR, Richmond BO: What I Think and Feel: a revised measure of children's manifest anxiety. *J Abnorm Child Psychol* 1978; 6:271-280
28. Reynolds CR: Concurrent validity of What I Think and Feel: the revised Children's Manifest Anxiety Scale. *J Consult Clin Psychol* 1980; 48:774-775
29. Reynolds HT: *The Analysis of Cross-Classifications*. New York, Macmillan, 1977
30. Conover WJ: *Practical Nonparametric Statistics*, 2nd ed. New York, John Wiley & Sons, 1980
31. Carlson GA, Cantwell DP: Suicidal behavior and depression in children and adolescents. *J Am Acad Child Psychiatry* 1982; 21:361-368
32. Rutter M: The developmental psychopathology of depression: issues and perspectives, in *Depression in Young People*. Edited by Rutter M, Izard CE, Read PB. New York, Guilford Press, 1986
33. Kashani JH, Hooper EW, Beck NC, et al: Personality, psychiatric disorders and parental attitude among a community sample of adolescents. *J Am Acad Child Adolesc Psychiatry* 1987; 26:879-889

Psychosocial Distress and Well-Being Among Gay and Bisexual Men With Human Immunodeficiency Virus Infection

Henry T. Chuang, M.D., Gerald M. Devins, Ph.D., John Hunsley, Ph.D.,
and M. John Gill, M.B.

The authors examined levels of psychosocial distress and well-being in 65 gay or bisexual men infected with the human immunodeficiency virus (HIV); 24 of these men had asymptomatic HIV infection, 22 had acquired immune deficiency syndrome (AIDS)-related complex, and 19 had AIDS. All of the men evidenced high levels of psychosocial distress, but those with AIDS-related complex and those with asymptomatic HIV infection were significantly more distressed than those with AIDS. Corresponding differences were not observed in feelings of psychosocial well-being. The authors conclude that specific psychosocial issues and adaptive demands should be identified over the course of HIV illness.

(Am J Psychiatry 1989; 146:876-880)

The impact of human immunodeficiency virus (HIV) infection can be devastating, both for those infected and for their friends and families (1-3). The stress involved is multifaceted. HIV infection is life-long, typically results in both physical and neurological deterioration, and carries a very high mortality rate. It can also lead to rejection of infected individuals because of fear of contagion and/or prejudice, particularly because it has mainly affected socially outcast minority groups (4-7). Initial work concerning the psychosocial aspects of HIV infection has focused on the distress experienced by individuals with acquired immune deficiency syndrome (AIDS). Investigators in various geographic locations (3, 8-11) have consistently found that many AIDS patients experience elevated levels of anxiety and depression severe enough to

warrant DSM-III diagnoses of adjustment disorder or major depression.

Research concerning psychosocial aspects of HIV infection (12-14; unpublished 1986 papers by A. Gattozzi and L. Temoshok et al.) has begun to examine two additional dimensions. One line of such research has been to compare the reactions and concerns of AIDS patients with those of terminally ill cancer patients. The aim of this work has been to establish the psychosocial impact of AIDS relative to that of other life-threatening illnesses. Findings have generally indicated that the anxiety, depression, and illness-related concerns of AIDS patients are similar in many ways to those of individuals affected by cancer (12, 13; unpublished 1986 papers by A. Gattozzi and L. Temoshok et al.). The second line of research has examined psychosocial adjustment among individuals with AIDS-related complex. Such research is vital because the needs of this group have largely been overlooked in the development of mental health services (13). Findings to date have indicated that patients with AIDS-related complex experience significantly greater distress than do those with AIDS (3, 14; unpublished 1986 papers by A. Gattozzi and L. Temoshok et al.), perhaps due to greater uncertainties about the course of the illness (unpublished 1986 paper by A. Gattozzi). Although this research has made a substantial contribution, it has relied on relatively small samples, has not included standardized, widely used psychological tests as indicators of distress, and has examined only individuals with AIDS-related symptoms. More recent efforts have begun to correct these problems; however, this work does not yet appear to have been reported in widely available outlets (15; unpublished 1988 paper of J. Rundell et al. and unpublished 1986 paper of L. Temoshok).

A logical extension of this line of research would involve an examination of psychosocial adjustment across the spectrum of HIV illness, including individuals who have been infected with HIV but who have not yet developed clinical signs or symptoms as well as those with AIDS-related complex and AIDS. To our knowledge, there has been only one published study examining the psychosocial adjustment of patients

Received Aug. 19, 1988; revision received Dec. 20, 1988; accepted Jan. 5, 1989. From the Departments of Psychiatry, Psychology, and Medicine, University of Calgary. Address reprint requests to Dr. Devins, Health and Behavior Project, Department of Psychology, University of Calgary, 2500 University Drive, N.W., Calgary, Alberta, Canada T2N 1N4.

Supported in part by the National Health Research and Development Program through a National Health Research Scholar Award to Dr. Devins.

Copyright © 1989 American Psychiatric Association.

across these three clinical milestones (16). That study, which involved homosexual men, found that 56% of those with AIDS, 78% of those with AIDS-related complex, and 39% of those with asymptomatic HIV infection met *DSM-III* criteria for adjustment disorder with anxiety, depression, or both. Thus, a significant proportion of patients with asymptomatic HIV infection experience severe distress and may require professional mental health care. More research is clearly needed to determine the psychosocial repercussions of the continuum and progression of HIV disease.

Research to date has focused exclusively on psychosocial distress. However, many HIV-infected individuals are able to adjust to their medical condition without experiencing disabling psychosocial problems; indeed, some succeed in maintaining or improving the quality of their lives (13). Research focused only on distress among infected individuals may thus result in an inaccurate representation of their overall psychosocial adjustment. It would be important, therefore, to examine psychosocial well-being as well as distress to obtain a more balanced assessment.

The present study was conducted to describe and compare psychosocial distress and well-being across three clinical milestones over the course of HIV illness. Because they represent the majority of individuals currently affected by the HIV epidemic, participants were limited to homosexual and bisexual male patients diagnosed as having asymptomatic HIV infection, AIDS-related complex, or AIDS. Widely used measures of psychosocial distress and well-being were administered in a standardized interview, and data concerning demographic status, recent life stress, and social networks were obtained for statistical control purposes.

METHOD

Participants were sampled from three patient groups corresponding to three clinical milestones in the course of HIV-related illness (17). The first group (patients with asymptomatic HIV infection) consisted of 24 men who were found to be HIV positive by repeat enzyme-linked immunosorbent assay and Western blot tests but who had not yet displayed any of the signs or symptoms of HIV infection. The second group (patients with AIDS-related complex) included 22 men who, in addition to being HIV seropositive, had displayed characteristic signs (e.g., laboratory profiles indicating immunosuppression, anergy) and symptoms (e.g., lymphadenopathy, fever, night sweats, persistent diarrhea) of HIV infection but had no systemic opportunistic infections or tumors indicative of AIDS. The last group (patients with AIDS) included 19 men who had been clinically diagnosed as having AIDS (i.e., systemic opportunistic infection, Kaposi's sarcoma or other lymphomas, or severe wasting attributed only to AIDS). Diagnoses were established by an infectious disease specialist (M.J.G.) who has considerable experience in working with AIDS patients. All participants

TABLE 1. Background Information for Men With Asymptomatic HIV Infection, AIDS-Related Complex, or AIDS

Variable	HIV (N=24)	AIDS- Related Complex (N=22)	AIDS (N=19)	Total
Education				
Some secondary	3	6	1	10
Completed secondary	6	4	6	16
Some post-secondary	4	4	5	13
Completed post-secondary	7	6	6	19
Some graduate	2	0	0	2
Completed graduate	0	2	1	3
Marital status				
Never married	12	16	8	36
Married	3	0	0	3
Separated	0	1	0	1
Divorced	0	0	2	2
Common-law marriage, gay relationship	9	5	8	22
Employment status				
Employed full-time	15	7	2	24
Employed part-time	0	2	1	3
Unemployed	4	10	14	28
Student	5	3	1	9
Retired	0	0	1	1
Living arrangements				
Alone	6	7	4	17
With parents or other relatives	3	5	3	11
With spouse or lover	10	5	8	23
With friends	4	5	4	13
With roommate	1	0	0	1
Religion				
Roman Catholic	5	4	1	10
Protestant	15	14	9	38
Atheist or agnostic	4	4	9	17
Income				
Less than \$20,000	10	16	11	37
\$20,000-\$39,999	8	6	5	19
Greater than \$40,000	3	1	2	6
Social networks				
Low	5	7	5	17
Medium	14	15	10	39
Medium-high	3	0	2	5
High	1	0	1	2

were men and were homosexual and/or bisexual in orientation and practice. They included all male HIV patients in treatment at our university outpatient clinic between March 1987 and July 1988.

The mean \pm SD age of the 65 men was 32.3 ± 8.56 years. For the 24 men with asymptomatic HIV infection it was 32.7 ± 9.79 ; for the 22 men with AIDS-related complex it was 30.5 ± 5.12 ; and for the 19 men with AIDS it was 34.7 ± 10.05 . Other demographic characteristics of the three groups are presented in table 1.

Psychosocial distress and well-being were assessed by using a battery of standardized and widely used psychological tests. These included 1) the Center for Epidemiologic Studies Depression Scale (CES-D Scale) (18) as an index of depressive symptoms, 2) the Profile of Mood States (POMS) (19) as an indicator of mood

disturbance, 3) the trait anxiety subscale of the State-Trait Anxiety Inventory (20) as a measure of general anxiety levels, 4) the Affects Balance Scale (21) as a measure of positive and negative affect, 5) the Hopelessness Scale (22) as an index of generalized pessimism, 6) a life happiness rating scale (23), and 7) a single item concerning the frequency of suicidal ideation during the preceding week (we developed this item, phrasing it in a format similar to the CES-D Scale items to which it was appended). A number of variables were also assessed to gain a better understanding of the groups and for possible statistical control purposes (covariance analyses). These included the patient's age, religious affiliation, educational level, marital status, employment status, living arrangements, and annual family income. The Social Networks Index (24) was also administered to obtain an indication of the extent of currently available social networks. A checklist of recent stressful life events (25) was also administered.

Data were obtained through structured interviews conducted by a psychiatrist (H.T.C.) with extensive clinical experience with AIDS patients. Interviews were conducted at least 4 weeks after the diagnoses had been established and communicated to patients. On average, each interview required approximately 60 minutes to complete. The nature of the study was explained to the patients, and none of those who were asked to volunteer their participation refused.

RESULTS

Data analyses were performed by using one-factor (Diagnostic Group) analyses of variance (ANOVA) or covariance (ANCOVA). Preliminary analyses were conducted to establish whether any of the demographic, social network, or stressful life event variables might have been related significantly to the dependent measures of psychosocial distress and/or well-being. Any variable that was discovered to be significantly related and met minimum criteria (e.g., $r > 0.30$) (26) was retained for statistical control as a covariate.

Overall, substantially elevated levels of psychosocial distress characterized patients in all three of the groups (see table 2). This did not appear to be paralleled, however, by severely compromised levels of psychosocial well-being. Rather, participants in each of the three groups reported an even balance of negative and positive affects. Suicidal ideation also appeared to be a relatively infrequent occurrence across the groups.

Statistical comparisons indicated that psychosocial distress and well-being differed significantly across the three clinical groups (table 3). The major difference appeared to occur between patients with AIDS and the combined group of patients with asymptomatic HIV infection and AIDS-related complex. Patients with asymptomatic HIV infection and AIDS-related complex evidenced significantly greater levels of depressive symptoms, mood disturbance, and trait anxiety than

TABLE 2. Psychosocial Well-Being and Distress of Men With Asymptomatic HIV Infection, AIDS-Related Complex, or AIDS

Variable	HIV Infection (N=24)	AIDS-Related Complex (N=22)	AIDS (N=19)	Total
CES-D Scale depression score	21.6	23.9	13.4	20.0
POMS mood disturbance score	50.6	62.7	21.6	46.5
State-Trait Anxiety Inventory trait anxiety score	46.1	45.2	35.1	42.6
Hopelessness Scale score	14.0	14.7	14.8	14.5
Suicidal ideation	0.4	0.4	0.4	0.4
Affects Balance Scale score	5.1	4.4	6.3	5.2
Life happiness rating scale score	6.8	6.7	7.9	7.1

TABLE 3. Analyses of Variance and Covariance in Psychosocial Well-Being and Distress Among Men With Asymptomatic HIV Infection, AIDS-Related Complex, or AIDS

Variable	F	df	Significant Group Differences ^a
CES-D depression score ^b	5.0 ^c	2, 62	HIV=AIDS-related complex>AIDS
POMS mood disturbance score ^d	6.7 ^c	2, 59	HIV=AIDS-related complex>AIDS
State-Trait Anxiety Inventory trait anxiety score	7.9 ^c	2, 62	HIV=AIDS-related complex>AIDS
Hopelessness Scale score	<1.0	2, 58	
Suicidal ideation	<1.0	2, 56	
Affects Balance Scale score ^d	2.4 ^c	2, 61	AIDS-related complex<AIDS
Life happiness rating scale score	<1.0	2, 57	

^aAs indicated by post hoc Tukey tests.

^bCovariate=Social Networks Index.

^c $p < 0.01$.

^dCovariate=recent negative life events.

^e $p < 0.10$.

did patients with AIDS. Patients with AIDS-related complex also reported a marginally significantly more negative balance of positive and negative affects than did those with AIDS. However, patients with asymptomatic HIV infection and patients with AIDS-related complex did not differ significantly on any of the measures of psychosocial distress or well-being. No significant differences were detected across any of the groups in generalized feelings of hopelessness, suicidal ideation, or ratings of overall life happiness.

DISCUSSION

The psychosocial distress that has been reported to occur among AIDS patients also appears to occur among individuals at earlier points in the progression of HIV disease. Indeed, in comparing distress across

the three groups represented in the design of our study, it appears that patients with asymptomatic HIV infection and patients with AIDS-related complex may actually experience higher levels of distress than do those with full-blown AIDS. It is likely that different psychosocial issues and adaptive demands emerge over the course of the illness. Although the endpoint of AIDS may force an individual to deal with such issues as death, dying, and the resolution of unfinished business (27), earlier stages may introduce equally—if not more—threatening stressors, such as uncertainties about the progression of the illness, fears of pain and suffering, social isolation and rejection, and more general fears of the unknown. Individuals with AIDS-related complex may be especially vulnerable because their symptoms serve as a constant reminder of their condition and its prognosis while simultaneously compromising social and occupational functioning (28). Therefore, psychotherapeutic interventions should be extended to patients across the full spectrum of HIV disease. Such efforts must recognize, however, that the critical issues may differ across clinical milestones.

Many of our participants experienced high levels of psychosocial distress. However, this did not appear to compromise the balance of their feelings of well-being so severely that all positive affect was eliminated. Overall, our patients reported a relatively balanced experience of negative and positive affects, with slight variations across the three clinical groups. It may be relevant, in this regard, that all of the patients received treatment within the Canadian socialized health care system, in which hospital care and clinical follow-up are virtually free of charge. Moreover, a relatively extensive network of social agencies, volunteer and self-help groups, and government-operated community mental health centers was available to meet their psychosocial needs. Such resources may have buffered the psychosocial impact of the illness (29).

The finding of an overall balance of positive and negative affects is consistent with the assertion that individuals are capable of coming to terms with the psychosocial threats imposed by chronic life-threatening illness and that the benefits of psychotherapeutic efforts can be enhanced by incorporating existing strengths (27, 30). It also underscores the importance of integrating both well-being and distress in any analysis of the psychosocial impact of HIV illness.

The issue of suicide has been raised in the context of the HIV epidemic, and, to date, reports have been conflicting. Some investigators (31, 32) have asserted that suicidal ideation is common among AIDS patients but that actual attempts are not as frequent. Others (33, 34) have reported that the risk of suicide is strikingly higher among people with AIDS than in the physically healthy population but have noted that many AIDS-related suicides appear to be sudden and impulsive. Suicidal ideation appeared to occur infrequently in our sample. One of our patients with AIDS-related complex, however, succeeded in completing suicide (under

the influence of alcohol) 8 months after participating in the study. Although he denied having experienced any suicidal ideation during the week preceding his participation in the study, his test scores at the time indicated high levels of depression, hopelessness, mood disturbance, and recent stressful life events. Thus, suicidal risk may be especially difficult to predict over the course of HIV illness and should be monitored regularly (34).

Although the three patient groups selected to represent the spectrum of HIV illness in our design do not correspond identically to the most recent Centers for Disease Control classification system (35), our groupings were conceptualized to represent distinct clinical milestones that are widely recognized as different points along the spectrum of HIV disease (17) and that can be clearly differentiated by patients. We believe that patients' interpretations of their medical status are most relevant to psychosocial distress and well-being and that their perceived progression along this continuum is more psychologically meaningful than their status in terms of formal diagnostic categories. Future research should focus on identifying the specific psychosocial issues and adaptive demands introduced by each of the clinical milestones over the course of HIV illness. Longitudinal research designs that incorporate a developmental theoretical approach may be best suited to this task.

REFERENCES

1. Frierson RL, Lippmann SB, Johnson J: AIDS: psychological stresses on the family. *Psychosomatics* 1987; 28:65-68
2. Rosser BRS, Ross MW: Perceived emotional and life change impact of AIDS on homosexual men in two countries. *Psychol Health* 1988; 2:301-317
3. Tross S, Hirsch DA: Psychological distress and neuropsychological complications of HIV infection and AIDS. *Am Psychol* 1988; 43:929-934
4. Britton S: Psychological aspects of HTLV-III infection. *Scand J Soc Med* 1986; 14:211-212
5. Cassens BJ: Social consequences of the acquired immune deficiency syndrome. *Ann Intern Med* 1985; 103:768-771
6. Dille JW, Shelp EE, Batki SL: Psychiatric and ethical issues in the care of patients with AIDS. *Psychosomatics* 1986; 27:562-566
7. McKusick L (ed): *What to Do About AIDS: Physicians and Mental Health Professionals Discuss the Issues*. Berkeley, University of California Press, 1986
8. Holland JC, Tross S: The psychosocial and neuropsychiatric sequelae of the acquired immunodeficiency syndrome and related disorders. *Ann Intern Med* 1985; 103:760-764
9. Dille JW, Ochitill HN, Perl M, et al: Findings in psychiatric consultations with patients with acquired immune deficiency syndrome. *Am J Psychiatry* 1985; 142:82-86
10. Frierson RL, Lippmann SB: Psychologic implications of AIDS. *Am Fam Physician* 1987; 35:109-116
11. Hoffman AS: Impact of AIDS. *Hosp Community Psychiatry* 1986; 37:943-944
12. Wolcott DL, Namir S, Fawzy FI, et al: Illness concerns, attitudes towards homosexuality, and social support in gay men with AIDS. *Gen Hosp Psychiatry* 1986; 8:395-403
13. Mandel JS: Psychosocial challenges of AIDS and ARC: clinical and research observations, in *What to Do About AIDS: Physicians and Mental Health Professionals Discuss the Issues*. Ed-

- ited by McKusick L. Berkeley, University of California Press, 1986
14. Goldmeier D: Psychosocial aspects of AIDS. *Br J Hosp Med* 1987; 37:232-240
 15. Tross S, Holland J, Hirsch DA, et al: Psychological and social impact of AIDS spectrum disorders, in *Proceedings of the Second International Conference on Acquired Immunodeficiency Syndrome (AIDS)*. Paris, Voyage Conseil, 1986
 16. Selwyn PA: AIDS: what is now known—IV: psychological aspects, treatment prospects. *Hosp Practice Off* 1986; 21(10): 125-130, 133, 137-138
 17. Slim J: The HIV is positive: what next? *Diagnosis* 1988; 5(7): 74-83
 18. Radloff LS: The CES-D scale: a new self-report depression scale for research in the general population. *Applied Psychol Measurement* 1977; 1:385-401
 19. McNair DM, Lorr M, Droppleman LF: *Manual for the Profile of Mood States*. San Diego, Educational and Industrial Testing Service, 1971
 20. Spielberger CD, Gorsuch RL, Lushene RE: *STAI Manual*. Palo Alto, Calif, Consulting Psychologists Press, 1970
 21. Bradburn NM: *The Structure of Psychological Well-Being*. Chicago, Aldine, 1969
 22. Beck AT, Weissman A, Lester D, et al: The measurement of pessimism: the Hopelessness Scale. *J Consult Clin Psychol* 1974; 42:861-865
 23. Atkinson T: Is satisfaction a good measure of the perceived quality of life? *Proc Am Stat Assoc* 1978; 123-132
 24. Berkman LF, Syme SL: Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *Am J Epidemiol* 1979; 109:186-204
 25. Devins GM, Mandin H, Hons RB, et al: Illness intrusiveness and quality of life in end-stage renal disease: comparison and stability across treatment modalities. *Health Psychol* (in press)
 26. Pedhazur EJ: *Multiple Regression in Behavioral Research: Explanation and Prediction*, 2nd ed. New York, Holt Rinehart & Winston, 1982
 27. Kubler-Ross E: *AIDS: The Ultimate Challenge*. New York, Macmillan, 1987
 28. Morin SF, Charles KA, Maylon AK: The psychological impact of AIDS on gay men. *Am Psychol* 1984; 39:1288-1293
 29. Beiser M, Shore JH, Peters R, et al: Does community care for the mentally ill make a difference? a tale of two cities. *Am J Psychiatry* 1985; 142:1047-1052
 30. McKusick L: The impact of AIDS on the practitioner and client: notes for the therapeutic relationship. *Am Psychol* 1988; 43: 935-940
 31. Faulstich ME: Psychiatric aspects of AIDS. *Am J Psychiatry* 1987; 144:551-556
 32. Macks J, Turner D: Mental health issues of persons with AIDS, in *What to Do About AIDS: Physicians and Mental Health Professionals Discuss the Issues*. Edited by McKusick L. Berkeley, University of California Press, 1986
 33. Frierson RL, Lippmann SB: Suicide and AIDS. *Psychosomatics* 1988; 29:226-231
 34. Marzuk PM, Tierney H, Tardiff K, et al: Increased risk of suicide in persons with AIDS. *JAMA* 1988; 259:1333-1337
 35. Classification system for human T-lymphotropic virus type III/lymphadenopathy-associated virus infections. *MMWR* 1986; 35:334-339

Private and Public Psychiatry: A Comparison of Two Health Care Systems

Gavin Andrews, M.D., F.R.C.Psych., F.R.A.N.Z.C.P.

Psychiatrists in Australia and New Zealand are similarly trained, but the health care delivery systems in each country differ. Australia has unlimited insurance for fee-for-service private practice and has twice the psychiatrists and half the psychiatric beds per capita as New Zealand. Psychiatrists in the public sector in each country focus on hospital-based care of psychotic patients. Private-sector psychiatrists, in addition to caring for psychotic patients, also focus on psychotherapy for neuroses and personality disorders. The Australian combination of more psychiatrists in private office practice and fewer public hospital beds costs less than the New Zealand system, which supports only public-sector, hospital-based services.

(Am J Psychiatry 1989; 146:881-886)

There is increasing international agreement in psychiatry about the criteria for each diagnosis and about the treatments to be preferred for each disorder. Major differences in patient management often depend more on the health delivery system than on different ideas about diagnosis and treatment. In this paper, the work of psychiatrists in Australia (1) and New Zealand (2), who spend an average of 80% of their time in clinical care, will be compared. The differences in the patterns of clinical care in the two countries shed light on the role of private fee-for-service practice, which, in Australia particularly, has developed because 85% of fees are reimbursed from a universal health insurance fund.

Australia has 16.2 million inhabitants; 12% live on farms, 63% live in cities with more than 100,000 people, and more than 80% of the population are of European, largely British, descent. New Zealand has 3.3 million inhabitants; 16% live on farms, 50% live in cities larger than 100,000, and, as in Australia, more than 80% of the population are of European, largely

British, descent. The education of psychiatrists in both countries follows a British model and leads, after 5 years of postgraduate training, to all candidates taking a common examination conducted by the Royal Australian and New Zealand College of Psychiatrists. In both countries about 85% of all psychiatrists have this qualification, with most of the remainder having a British qualification. Thus, the people, the culture, and the training of psychiatrists in both countries are remarkably similar.

In the present paper the work of psychiatrists in the two countries will be compared and related to the number of psychiatrists, number of psychiatric beds, and the health care delivery systems, including a comparison between private fee-for-service and public-salaried practice in each country.

METHOD

In Australia a one-in-six sample of psychiatrists was formed in 1981 to participate in a 5-year study of treatment practices (3). In 1986 the 167 remaining in the sample were asked to take part in the present study. In 1987 all 142 members or fellows of either the Royal Australian and New Zealand College of Psychiatrists or the Royal College of Psychiatrists who had a New Zealand mailing address were contacted; 111 were in active clinical practice and were asked to participate. Each physician was asked for details of the last 20 patients seen prior to given dates, and each was assured that in addition to the fact that no details of patient identification were required, any identification with their practice would be removed when the questionnaires were returned.

The one-page questionnaire sought the following information about each of the 20 patients: 1) demographic characteristics, 2) primary and secondary diagnoses, 3) primary and secondary treatments used during the index consultation, 4) information about the present consultation (whether the patient was an inpatient or an outpatient, and whether the patient was seen in private or public practice), and 5) details of the past, present, and expected consulting histories. If the physician thought that this patient would "always need psychiatric care," this was coded as 150 months, one-third the life expectancy of the median patient.

Presented at a meeting of the World Psychiatric Association, Sydney, Australia, May 1-3, 1988. Received Aug. 17, 1988; revision received Dec. 21, 1988; accepted Jan. 12, 1989. From the University of New South Wales. Address reprint requests to Dr. Andrews, Clinical Research Unit for Anxiety Disorders, University of New South Wales at St. Vincent's Hospital, 299 Forbes St., Darlinghurst, NSW 2010, Australia.

Copyright © 1989 American Psychiatric Association.

The number of psychiatrists in practice in Australia was obtained from a report prepared for the Royal Australian and New Zealand College of Psychiatrists (4) and verified from our records. Early in 1988 the numbers of psychiatric beds (excluding beds reserved for patients with mental deficiency or with alcohol and drug problems) were obtained from the departments of health in each Australian state and from the New Zealand government. These numbers were verified by inquiry to psychiatrists in each geographical center. Population figures were provided by the respective government agencies.

RESULTS

There were 1,428 qualified psychiatrists in Australia, or 8.8 per 100,000 population. Fifty-five percent reported that they were predominantly in private practice, and 85% practiced in cities with more than 100,000 people. Australia in late 1987 had 12,086 hospital beds for psychiatric patients, a rate of 74 beds per 100,000. Mental hospitals accounted for 75% of these beds, general hospitals 14%, and private hospitals 12%.

In 1987 there were 142 psychiatrists with a New Zealand mailing address, or 4.3 per 100,000. Ten percent were predominantly in private practice and, as in Australia, the majority (77%) practiced in cities of over 100,000. New Zealand in late 1987 had 4,236 hospital beds for psychiatric patients, or 128 beds per 100,000. Mental hospitals accounted for 88% of these beds, general hospitals 10%, and private hospitals 2%. The distributions of facilities per capita in Australia and New Zealand are very different. Australia has twice the psychiatrists and half the beds per 100,000 as New Zealand. In broad terms, since half the psychiatrists in Australia are in fee-for-service private office practice, the number of psychiatrists in public-sector practice per capita in both countries is the same.

The results of the surveys of patients seen by psychiatrists are presented in tables 1 and 2; the totals vary because of a 5% missing data rate. The response rate in both countries was 59%: 99 of 167 in Australia, and 66 of 111 in New Zealand. In Australia the characteristics of physicians responding and not responding could be compared: they did not differ in terms of sex or type of practice (1). There were no direct data on the characteristics of the physicians who did not respond in the New Zealand study (2).

Of the Australian patients, 77% (1,471 of 1,909) were seen privately; the corresponding figure for New Zealand was 15% (183 of 1,202). In tables 1 and 2, data for the two countries are compared, with separate data being presented for private and public practice within each country. Comparisons that revealed significant differences are noted, and the alpha level was set at $p < 0.01$ after the multiple comparisons within each set or family of measures were allowed for.

At the time of the index consultation, 12% (225 of

1,893) of the Australian and 25% (313 of 1,256) of the New Zealand patients were inpatients, figures that parallel the availability of beds in each country. In both countries inpatient care was significantly associated with public-sector and not private-sector practice (New Zealand, $\chi^2 = 17.7$, $df = 1$, $p < 0.001$; Australia $\chi^2 = 342.6$, $df = 1$, $p < 0.001$). Physicians were asked to rate "the extent to which the condition interferes with this patient's life." Australian patients were judged to be 43% impaired and New Zealand patients 49% impaired, a difference attributable to public patients in both countries being judged to be one-third of a standard deviation more impaired than private patients.

The social and demographic characteristics of patients are shown in table 1. The age distributions in both countries are broadly similar, and in the public sector the proportions of elderly are the same, making it clear that the extra psychiatric beds in New Zealand are unlikely to be the result of different policies for the care of the elderly. The proportion of women consulting was higher in Australia. In both countries the physicians in the public sector saw nearly equal numbers of men and women, and physicians in the private sector saw more women. Patients in the work force were twice as likely to receive private care, and patients receiving Social Security pensions were twice as likely to attend public sector psychiatrists. However, within Australia, the universal reimbursement of physicians fees meant that a large number of Social Security pensioners were seen in the private sector. In New Zealand, fewer patients were married and more were living permanently in government-run homes or hospitals. Again, this is an effect of the large private sector in Australia, for in both countries living with a spouse is associated with seeing a private psychiatrist and living in a government-run home or hospital is associated with seeing a public sector psychiatrist.

The patients' primary diagnoses and the principal treatments given on the day the questionnaire was filled in are shown in table 1. There were consistent and significant differences in the frequencies of various diagnoses of patients seen in each country. In Australia half the patients seen suffered from neuroses or personality disorders and one-third suffered from psychoses; in New Zealand half suffered from psychoses and one-quarter from neuroses or personality disorders. In both countries, the majority of patients treated in the public sector had diagnoses of psychoses. In contrast 58% of Australian private-sector patients suffered from neuroses or personality disorders, and only 26% from psychotic disorders. In Australia, despite this bias and because of the size of the private sector, more patients with psychoses were seen in the private sector than in the public sector.

Only the principal treatment used for each patient was coded. Treatment followed diagnosis in a predictable way (see table 1). Australian physicians used more psychotherapy and New Zealand physicians more drug therapy, but again the patterns in public-sector

Table 1. Demographic Characteristics, Diagnoses, and Treatments of Public and Private Patients of 99 Psychiatrists in Australia and 62 Psychiatrists in New Zealand^a

Item	Australian Patients				New Zealand Patients				Total			
	Public (N=438) ^b		Private (N=1,471) ^b		Public (N=1,019) ^b		Private (N=183) ^b		Australian (N=1,940) ^b		New Zealand (N=1,292) ^b	
	N	%	N	%	N	%	N	%	N	%	N	%
Demographic characteristics												
Age (years)												
0-16	51	11.8	87	5.9 ^c	93	9.2	4	2.2	139	7.2	103	8.1
17-64	339	78.1	1,308	89.4 ^c	827	81.4	158	86.3	1,675	86.9	1,053	82.4 ^c
65 and older	44	10.1	68	4.6	96	9.4	21	11.5	114	5.9	122	9.5 ^c
Sex												
Male	222	51.0	521	35.0	467	46.0	77	42.0	754	39.0	587	46.0
Female	216	49.0	948	65.0 ^d	546	54.0	106	58.0	1,184	61.0	690	54.0 ^d
Occupation												
Higher status	20	4.6	296	20.1 ^c	36	3.5	22	12.0 ^c	320	16.2	62	4.7 ^e
Lower status	60	13.7	437	29.7 ^c	266	26.1	82	44.8 ^c	504	25.5	377	28.6
Home duties	74	16.9	254	17.3	155	15.2	33	18.0	336	17.0	203	15.4
Student	54	12.3	139	9.4	121	11.9	7	3.8 ^e	195	9.8	138	10.5
Pensioner (not elderly)	174	39.7	259	17.6 ^c	309	30.3	17	9.3 ^e	442	22.3	340	25.8
Retired or other	53	12.1	81	5.5 ^e	120	11.8	20	10.9	135	6.8	146	11.1 ^c
Living arrangements												
Alone	66	17.3	237	17.4	181	18.2	32	17.8	308	17.4	225	17.9
With family or friends	136	35.7	442	32.5	388	39.0	45	25.0 ^f	587	33.2	464	37.0
With spouse	130	34.1	654	48.1 ^f	327	32.9	100	55.6 ^f	797	45.1	457	36.4 ^f
In hostel or hospital	49	12.9	25	1.8 ^f	97	9.8	3	1.7 ^f	74	4.2	107	8.5 ^f
Primary diagnosis												
Psychosis	228	52.2	379	25.9 ^d	564	55.5	79	43.4	618	32.0	683	53.4 ^d
Depression and/or mania	75	17.2	252	17.2	314	30.9	61	33.5	335	17.3	399	31.2 ^c
Schizophrenia	115	26.3	96	6.6 ^c	199	19.6	13	7.1 ^c	213	11.0	222	17.3 ^c
Organic or other disorder	38	8.7	31	2.1 ^c	51	5.0	5	2.7	70	3.6	62	4.8
Neurosis or personality disorder	116	26.6	845	57.8 ^d	247	24.3	61	33.5	976	50.5	325	25.4 ^d
Depressive neurosis	21	4.8	225	15.4 ^f	66	6.5	15	8.2	248	12.8	85	6.6 ^f
Anxiety or phobic neurosis	31	7.1	253	17.3 ^f	49	4.8	30	16.5 ^f	289	15.0	84	6.6 ^f
Other neurosis	48	11.0	137	9.4	65	6.4	9	4.9	192	9.9	77	6.0 ^f
Personality disorder	16	3.7	230	15.7 ^f	67	6.6	7	3.8	247	12.8	79	6.2 ^f
Marital problems or no axis II diagnosis (DSM-III code V79.01)	26	5.9	94	6.4	34	3.3	19	10.4 ^d	122	6.3	64	5.0
Other	67	15.3	147	10.0	172	16.9	23	12.6	217	11.2	208	16.3 ^d
Primary treatment												
Drug therapy	189	43.8	353	24.2 ^d	445	44.2	69	38.5	553	28.8	547	43.2 ^d
Antidepressant	49	11.3	161	11.0	161	16.0	36	20.1	213	11.1	207	16.3 ^g
Anxiolytic	8	1.9	17	1.2	9	0.9	2	1.1	25	1.3	11	0.9
Antipsychotic	54	12.5	58	4.0 ^g	84	8.3	6	3.4	113	5.9	98	7.7
Unspecified	63	14.6	97	6.6 ^g	139	13.8	14	7.8	166	8.6	163	12.9 ^g
Other	15	3.5	20	1.4	52	5.2	11	6.1	36	1.9	68	5.4 ^g
Psychotherapy	160	37.0	977	66.7 ^d	408	40.5	86	48.1	1,150	59.9	531	41.8 ^d
Insight-oriented	2	0.5	163	11.1 ^c	13	1.3	18	10.1 ^c	165	8.6	31	2.4 ^c
Supportive	83	19.2	335	22.9	227	22.5	46	25.7	423	22.0	296	23.3
Behavior therapy	10	2.3	42	2.9	16	1.6	8	4.5	53	2.8	27	2.1
Family, marital, or group	25	5.8	76	5.2	45	4.5	1	0.6	104	5.4	53	4.2
Other	11	2.5	27	1.8	34	3.4	2	1.1	38	2.0	38	3.0
Unspecified	29	6.7	334	22.8 ^c	73	7.2	11	6.1	367	19.1	86	6.8 ^c
Other	83	19.2	132	9.0 ^d	155	15.4	24	13.4	222	11.5	190	15.0

^aTotals vary because of a 5% missing data rate.^bPercents are based on the number of patients for whom data were available, rather than on the total number of patients in each group.^cp<0.01 by chi-square, df=1, allowing for three comparisons in the family of variables.^dp<0.01 by chi-square, df=1, allowing for one comparison in the family of variables.^ep<0.01 by chi-square, df=1, allowing for six comparisons in the family of variables.^fp<0.01 by chi-square, df=1, allowing for four comparisons in the family of variables.^gp<0.01 by chi-square, df=1, allowing for five comparisons in the family of variables.

practice in both countries were very similar. Insight-oriented, or intensive, dynamically oriented, psychotherapy was virtually confined to the private practice sector in both countries.

The pattern of consultation was the next area to be examined (see table 2). Australian psychiatrists saw their patients more often, for longer at each consultation, and, in total, anticipated spending twice as many

Table 2. Length of Treatment of Public and Private Patients of 99 Psychiatrists in Australia and 62 Psychiatrists in New Zealand^a

Length of Treatment	Australian Patients				New Zealand Patients				Total			
	Public (N=438)		Private (N=1,471)		Public (N=1,019)		Private (N=183)		Australian (N=1,940)		New Zealand (N=1,292)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Time between first visit and index visit (months)	22.0	32.0	20.0	28.0	18.0	28.0	13.0	22.0 ^b	20.0	29.0	18.0	27.0
Duration of index visit (minutes)	30.0	19.0	49.0	18.0 ^b	35.0	21.0	38.0	19.0	45.0	20.0	36.0	21.0 ^b
Frequency of consultations per month	1.2	1.3	2.2	2.8 ^b	1.3	1.6	1.6	2.2	2.0	2.5	1.3	1.7 ^b
Expected time until patient would no longer need psychiatric care (months)	79.0	67.0	43.0	56.0 ^b	60.0	65.0	43.0	57.0 ^b	51.0	60.0	56.0	63.0
Expected total length of treatment (hours)	48.0	72.0	118.0	241.0 ^b	50.0	87.0	43.0	76.0 ^b	101.0	215.0	48.0	84.0 ^b

^aTotals vary because of a 5% missing data rate.^bp<0.01, two-tailed t tests, allowing for five comparisons in each family of variables.

hours with them. All these differences could be attributed to the pattern of Australian private psychiatric practice, for the consulting patterns in public practice in both countries were very similar.

DISCUSSION

These data allow a comparison between two health delivery systems that both provide free inpatient and outpatient care in public general hospitals and in mental hospital facilities. Coverage for private hospital inpatient care requires additional voluntary insurance, and this is taken out by only a minority of people in both countries. In New Zealand there is minimal coverage for private physicians' fees, whereas Australia has had a system of voluntary insurance for private physicians' fees for 20 years, and by 1983 more than 70% of the population were insured. In 1984 the federal government of Australia took over the management of this insurance and made reimbursement of 85% of an agreed fee available to the entire population. For specialist psychiatrists this fee is currently about \$100 (\$85 U.S.) per hour. This insurance support has encouraged the development of private office-based practice in Australia.

The definition of a psychiatric bed and the training of psychiatrists are identical in Australia and New Zealand. Diagnostic labels, at least within the broad level used in this study, are consistent with ICD-9 even though the influence of *DSM-III* has been profound. Because of the similar training in both countries and because of the publication of the treatment outline project (3) in the years preceding this survey, there is a large measure of agreement as to the labels to be used to describe various treatments. Data on manpower and bed numbers were cross-checked from at least two sources of information until consensus was achieved. Evidence on the validity and reliability of the physicians' reports on the 20 patients they saw prior to the start date of the surveys has been published (1, 2).

Given that the data may be valid, what conclusions can be drawn? New Zealand and Australia have similar public-sector psychiatric services, each with four psychiatrists per 100,000 who see a third of their patients in the hospital—patients who are unlikely to be in the work force and who are likely to suffer from a psychotic illness. In Australia there is, in addition, a large private psychiatry sector that treats patients who are less impaired and more likely to be in the work force. Even so, physicians in the private sector see more patients with psychoses than do physicians in the public sector, make less use of inpatient facilities, and give many more hours of psychotherapy to patients with neuroses and personality disorders. These differences are also evident in the small New Zealand private sector, although the lack of manpower must mean that some patients with psychoses and many patients with neurotic and personality disorders remain untreated.

In both countries the proportion of private consultations was larger than would be expected from the proportion of physicians believed to be in private practice. Since each physician reported on the last 20 patients seen, one conclusion is that some physicians in the public sector are also seeing patients on a fee-for-service basis. In Australia, 45% of physicians said they were in public practice (4), but in the present study only 10% (10 of 99) reported exclusively on patients from the public sector, 43% (43 of 99) reported seeing both private and public patients, and 47% (47 of 99) reported on private patients only. In New Zealand, 56% of physicians (35 of 62) reported seeing only public patients, 44% (27 of 62) saw both public and private patients, and no physician saw only private patients. Thus, in both countries, many public-sector psychiatrists are also seeing patients privately, a trend that could well be encouraged by appointing hospital staff on a genuinely part-time basis. The differences in health care funding may have influenced the availability of psychiatrists, for at the time of this study there was only one Australian graduate who had migrated to practice psychiatry in New Zealand, while 69 New

Zealand medical graduates were practicing psychiatry in Australia.

The costs of these two systems of health care delivery can be estimated. Australian private-sector psychiatrists in full-time practice gross \$150,000 (\$125,000 U.S.) on average, out of which they will pay for telephone, rooms, and secretarial assistance. The average private psychiatrist nets more than the average family physician, has a similar net income to nonprocedural internists, but has a net income less than that of procedural specialists like surgeons or obstetricians. Full-time public-sector psychiatrists receive salary packages that average \$70,000, to which should be added \$30,000 to cover the cost of telephone, rooms, and secretarial assistance. Thus, the average cost of a public-sector psychiatrist will be \$100,000/year. On the assumption that 55% of psychiatrists in Australia are in predominantly private practice, the cost of the average Australian psychiatrist is \$127,500/year. Since there are 8.8 per 100,000, the cost to the community can be calculated as \$1.12 million per 100,000 population. The cost of a public-sector psychiatrist in New Zealand is similar to that in Australia; thus, salary package and infrastructure costs total \$100,000/year. Private psychiatrists in New Zealand should probably be costed at a similar figure for the lack of insurance limits attainable earnings. New Zealand has 4.3 psychiatrists per 100,000, and so the cost of psychiatrists per 100,000 population can be calculated to be \$0.43 million.

The recurring costs of a hospital service calculated in available bed-day units can also be calculated. If an average of \$150 per day is used, the rate paid by health insurers to private hospitals for shared-ward long-stay accommodation, excluding the costs of drugs, investigations, and physicians fees, then Australia with 74 beds per 100,000 will pay \$4.05 million/year and New Zealand with 128 beds per 100,000 will pay \$7.0 million/year per 100,000 population for their hospital-based services. Using these figures, we can calculate the cost of psychiatric care in Australia at \$5.17 million/year per 100,000, while services modeled on the New Zealand system, calculated at \$7.43 million/year per 100,000, would be 44% more expensive.

If the goal of psychiatric care is to treat people in the community and maintain them as contributing members of society, then the Australian system appears to be both more effective and cheaper. With 74 beds per 100,000, Australia has one of the lowest bed ratios of any developed nation (5). In 1982, England and Wales had 2.4 psychiatrists and 187 beds per 100,000 (5), while data supplied by the American Psychiatric Association for 1982 suggest that the United States had 14 qualified psychiatrists and 108 beds per 100,000 population. Given such numbers of psychiatric beds, the U.S. system and the British system, in particular, would, if introduced into Australia, cost much more than the present Australian system, even though Aus-

tralia has universal and unlimited reimbursement of private physicians' fees.

In Australia the bed numbers are still being reduced and seem likely to decline to 50 beds per 100,000 or even lower. There are still large rural mental hospitals with static aging populations of patients, and closing these hospitals will reduce the bed ratios significantly. In a recent survey of discharged long-stay mental hospital patients (unpublished paper), we have shown that the vast majority prefer to live in the community no matter how Spartan the accommodation. In Sydney, a city of 3.5 million that has an active program of deinstitutionalization, the provision of community support services and the availability of psychiatrists have meant that few problems are posed by patients living in the community (our unpublished data). It is tempting to conclude that in Australia the need for beds has been reduced by the accessibility of psychiatrists in private community practice. Conversely, in New Zealand, where there are few psychiatrists and a large investment in mental hospital services, criticism of what happens in those hospitals is considerable, both in the lay press and in scientific journals (6).

Unlimited reimbursement of fees in the Australian system has been criticized because of the extent of long-term individual and group psychotherapy. I have argued elsewhere (1, 7) that, notwithstanding the value of long-term psychotherapy for many patients, some of the physicians carrying out such therapies have had no special training and some of the patients, being in high status jobs, seem unlikely to be still handicapped by the condition for which they are receiving therapy. A threshold beyond which reimbursement from insurance funds would cease, unless justified by both the clinical need of the patient and the competence of the therapist, would solve this problem. Disputed cases could be resolved using a peer review process similar to that used by the American Psychiatric Association.

The present study has attempted to integrate comparative data on manpower and bed ratios with information about clinical practice and type of payment systems. The Australian system, which provides unlimited reimbursement of fee-for-service office practice, has always been regarded as very expensive. However, such a system has encouraged psychiatrists to go into private practice in the community and allowed bed numbers to be reduced so that, in comparison to New Zealand, it has been possible to treat twice as many patients at two-thirds the cost. The Australian system appears to be relatively cost efficient and capable of fine tuning to produce an effective and efficient mental health care service.

REFERENCES

1. Andrews G, Hadzi-Pavlovic D: The work of Australian psychiatrists, circa 1986. *Aust NZ J Psychiatry* 1988; 22:153-165
2. Andrews G, Morris-Yates A: The workload of New Zealand psychiatrists. *NZ Med J* 1988; 101:753-755

3. Andrews G, Hadzi-Pavlovic D, Christensen H, et al: Views of practicing psychiatrists on the treatment of anxiety and somatoform disorders. *Am J Psychiatry* 1987; 144:1331-1334
4. Burvill PW: A survey of the distribution of psychiatrists in Australia and New Zealand in 1987. *Aust NZ J Psychiatry* 1988; 22:436-447
5. Freeman HL, Fryers T, Henderson JH: Mental Health Services in Europe: 10 Years On. Copenhagen, World Health Organization, 1985
6. Malcolm LA: Bed availability as a significant influence on rates of committal to New Zealand's psychiatric hospitals. *NZ Med J* 1989; 102:8-9
7. Andrews G: Psychotherapy and health insurance. *Aust NZ J Psychiatry* 1983; 17:68-72

Deceased Members of the American Psychiatric Association

The deaths of these members were reported to APA between Feb. 3 and April 5, 1989.

John T. Andersen, M.D.	Roy W. Goshorn, M.D.	John W. Mudd, M.D.
Herman M. Beerman, M.D.	Richard W. Gray, M.D.	George F. Newman, M.D.
Harold Birnkrant, M.D.	Rachel K. Gundry, M.D.	Irene A. Phrydas, M.D.
Waldemar H. Boldt, M.D.	Louis Jacobs, M.D.	Hyman Pleasure, M.D.
Harold Roy Brillinger, M.D.	Roland A.C. Jefferson, M.D.	Horace J. Prescod, M.D.
Sylvester T. Centrone, M.D.	Laszlo Kadar, M.D.	Curtis T. Prout, M.D.
Catherine Cullinan, M.D.	Albert Kandelin, M.D.	James H. Rumbaugh, M.D.
Desmond Curran, M.D.	Werner Kohlmeyer, M.D.	Robert F. Scott, M.D.
Frank J. Curran, M.D.	George Kojak, Jr., M.D.	Wayne Ray Shaw, M.D.
Howard Davidman, M.D.	Gustav Kol, M.D.	Jack Skigen, M.D.
Jean Delay, M.D.	Selig M. Korson, M.D.	Albert P. Spaar, Jr., M.D.
Sami Zakaria Demay, M.D.	Morris A. Lipton, Ph.D., M.D.	Isadore Tuerk, M.D.
Samuel T. Diaz, M.D.	Julius Loman, M.D.	Fausto R. Vitug, M.D.
William James S. Edington, M.D.	Joan Donna Longer, M.D.	Karl J. Waggner, M.D.
Emilio G. Espindola, M.D.	Clyde S. Marshall, M.D.	Stephen R. Walters, M.D.
Harrison Evans, M.D.	George J. Martin, M.D.	Francis J. Warner, M.D.
Ruth Fox, M.D.	James W. McGough, M.D.	Nathaniel Warner, M.D.
Curtis Uvell Franklin, Jr., M.D.	Hugh McHugh, M.D.	Simon Weyl, M.D.
Henry Freund, M.D.	John C. Mergener, M.D.	Helmut Yager, Ph.D., M.D.
N.J. George, M.D.	Hazel Schayes Mrazek, M.D.	

The Presumptive Role of Fantasy in Serial Sexual Homicide

Robert Alan Prentky, Ph.D., Ann Wolbert Burgess, R.N., D.N.Sc.,
Frances Rokous, B.A., Austin Lee, Ph.D., Carol Hartman, R.N., D.N.Sc.,
Robert Ressler, M.S., and John Douglas, M.S.

The authors examined the role of fantasy as an internal drive mechanism for repetitive acts of sexual violence. A sample of 25 serial sexual murderers with three or more known victims each was compared with a sample of 17 single sexual murderers, with only one known victim each. The drive mechanism was hypothesized to be an intrusive fantasy life manifested in higher prevalences of paraphilias, documented or self-reported violent fantasies, and organized crime scenes in the serial murderers. All three hypotheses were supported.

(Am J Psychiatry 1989; 146:887-891)

Among the four violent Crime Index offenses of the Federal Bureau of Investigation (FBI), murder is the most infrequent, accounting for about 2% of the total violent crimes. And of those who murder once, only a small fraction murder again (1). Within the overall category of murder, homicides that appear to be sexually motivated are uncommon (2, 3), and serial sexual homicide is even more infrequent. Despite the proportionately few serial sexual murderers, the number of victims accounted for by each perpetrator is often very high. For instance, Ressler et al. (4) reported on the 118 known victims of 36 sexual murderers. The consequent impact of this small but very violent subgroup of offenders is indeed large.

Of even greater concern is that the frequency of these random, seemingly motiveless, murders appears to be increasing (5). Burgess et al. (5) noted that between 1976 and 1984 there was a 160% increase in murders with unknown motives. Motivated murders

tend to have identifiable external precipitators; many of these murders are premeditated, intentional, rational acts or accidental killings committed in the heat of passion (6, 7). Sexual homicide, however, has typically been viewed as an anomalous event and has defied efforts to devise an explanatory model based on some theory-driven conceptualization of the behavior. In his classic paper on the subject, Brittain (8) disavowed any attempt at theoretical formulation and instead provided a descriptive profile of the sadistic murderer. Similarly, in his attempt to categorize sexual murderers, Revitch (9) described three cases (impulsive, compulsive, and catathymic or tension release) without positing any theory to explain the behavior.

MacCulloch et al. (10) provided a novel explanation of the motivation of 13 of the 16 sadistic patients they examined, whose crimes (not all homicide) appeared to be driven by "internal circumstances." MacCulloch et al. found a pattern of sadistic fantasies that, in repetition-compulsion fashion, were played out repeatedly—initially in fantasy only, later on in behavioral mock trials, and eventually in assaults. The more the fantasies were cognitively rehearsed, the more power they acquired.

The excellent descriptive case reports by Brittain (8), Revitch (9), MacCulloch et al. (10), and others have provided a rich source for hypothesis generation. In particular, MacCulloch et al. (10) underscored the critical importance of fantasy as a possible drive mechanism for extremely serious crimes that, until recently, were assigned to the wastebasket of "unknown motive." A number of plethysmography studies (11-13) provide support for the role of fantasy in perpetuating sexually assaultive behavior. As Abel and Blanchard noted, there is also abundant support in the psychoanalytic literature for the "high concordance between presence of deviant fantasies and occurrence of deviant behavior" (14, p. 468).

Burgess et al. (5) reported a fantasy-based motivational model for sexual homicide. The model, which has five interactive components (impaired development of attachments in early life; formative traumatic events; patterned responses that serve to generate fantasies; a private, internal world that is consumed with violent thoughts and leaves the person isolated and self-preoccupied; and a feedback filter that sustains repetitive thinking patterns), was tested on a sample of

Received April 25, 1988; revision received Dec. 15, 1988; accepted Feb. 2, 1989. From the Research Department, Massachusetts Treatment Center and Department of Psychiatry, Boston University School of Medicine; School of Nursing, University of Pennsylvania, Philadelphia; Department of Psychology, Yale University, New Haven, Conn.; Department of Mathematics, Boston University; School of Nursing, Boston College; and Behavioral Sciences Unit, Federal Bureau of Investigation, Quantico, Va. Address reprint requests to Dr. Prentky, Research Department, Massachusetts Treatment Center, Box 554, Bridgewater, MA 02324.

Supported by National Institute of Justice grant 82-IJ-CX-0058 and Office of Juvenile Justice and Delinquency Prevention grant 84-JW-AX-K010 from the U.S. Department of Justice, NIMH grant MH-32309, and the Commonwealth of Massachusetts.

Copyright © 1989 American Psychiatric Association.

36 sexual murderers. In that initial study, Burgess et al. (5) found evidence for daydreaming and compulsive masturbation in over 80% of the sample in both childhood and adulthood.

Using the same sample, Ressler et al. (4) examined the role of the organized/disorganized dichotomy (15), which has proven to be a relatively powerful discriminator in two important areas, crime scene investigation and life history variables. Classification of a crime as organized or disorganized is made with data present at the scene of a murder and is based on the notion that highly repetitive, planned, well-thought-out offenses will be distinguishable from spontaneous, random, sloppy offenses. According to Ressler et al.'s prediction (4), the organized offender should be more characterized by a fantasy life that drives the offenses than is the disorganized offender. Ressler et al. found numerous differences between organized and disorganized offenders with respect to acts committed during their offenses, thus providing support for the validity of a typological discrimination that has theoretical roots in fantasy.

A critical, yet untested, question concerns putative differences between serial and single sexual murderers. The present study was intended to examine the presumptive role of fantasy as a drive mechanism for repetitive (i.e., serial) sexual murder. The working hypothesis was that serial sexual murderers are more likely to have underlying internal mechanisms that drive their assaultive behavior than single sexual murderers. This internal drive mechanism was hypothesized to take the form of an intrusive fantasy life that is manifested in 1) a higher prevalence of paraphilias, 2) a higher prevalence of organized crime scenes, and 3) a higher prevalence of violent fantasies.

METHOD

Subjects

The sample of serial sexual murderers consisted of 25 of the 36 murderers from an earlier study by the FBI (4, 5, 16). Only men who had committed three or more sexual homicides each were included in this study. The men were interviewed by special agents of the FBI in various U.S. prisons between 1979 and 1983. The data collected included information retrieved from official records, e.g., psychiatric and criminal records, pretrial records, court transcripts, interviews with correctional staff, and prison records. The information derived from these structured interviews and archival sources was coded with a questionnaire.

The sample of single sexual murderers consisted of seven offenders in the FBI sample and 10 men residing at the Massachusetts Treatment Center; each had murdered only once. The data for the Massachusetts Treatment Center subjects were archival. The clinical files of men committed to the center include past institution-

TABLE 1. Descriptive Characteristics of Serial and Single Sexual Murderers^a

Characteristic	Serial (N=25)		Single (N=17)	
	N	%	N	%
Race				
Caucasian	24	96	14	82
Black	1	4	2	12
Marital status				
Married	5	21	3	20
Divorced or separated	7	29	5	27
Never married	12	50	9	53
IQ				
Above average (≥ 110)	14	58	4	29
Below average (≤ 90)	4	17	4	29
Age at time of first murder (years)				
<20	7	28	4	24
20-24	6	24	4	24
25-30	9	36	5	29
>30	3	12	4	24

^aSome data were missing for some individuals, so percentages were based on varying total numbers of subjects.

alization records, school and employer records, parole summaries, probation records, and social service notes. Since the initial evaluation process includes clinical interviews, psychological testing, and review of final records from court-appointed examiners, this information is available as well. After evaluation, substantial information is added to the file during treatment, including psychiatric evaluations and progress reports on all aspects of the rehabilitation program. The clinical files were coded with a questionnaire similar to the one employed in the FBI study.

Some demographic characteristics of the two samples are provided in table 1. The serial group was almost exclusively Caucasian, while about one-fifth of the single group was either black or Hispanic. Marital status was almost identical for the two groups. Since the age of the offender at the onset of violent criminal activity could be a critical factor, we compared the two samples' ages at the time of their first sexual homicides. As shown in table 1, the samples were remarkably similar ($\chi^2=1.02$, $df=3$, $p<0.80$). The only noteworthy comparison concerned intelligence; 58% of the serial murderers but only 29% of the single murderers had higher than average IQs, although the difference was not statistically significant ($\chi^2=3.14$, $df=2$, $p<0.21$). This trend is entirely consistent with theoretical expectations and essentially parallels the difference between the groups in organization of the crime scene. That is, it has been hypothesized (15) that organized murderers have higher IQs than disorganized murderers. While intelligence seems to have little bearing on the quality or content of the fantasy, it does influence how well the fantasy is translated into behavior (i.e., how organized the crime is) and how successfully the offender eludes apprehension.

Procedure

Fantasy is a rather inclusive term that covers a wide range of cognitive processes. Our use of the term "fantasy" in this paper is based on an information processing model that interprets thoughts as derivations of incoming stimuli that have been processed and organized (17). Daydreaming has been defined as any cognitive activity representing a shift of attention away from a task (18). A fantasy, as it is defined in this study, is an elaborated set of cognitions (or thoughts) characterized by preoccupation (or rehearsal), anchored in emotion, and originating in daydreams. A fantasy is generally experienced as a collection of thoughts, although the individual may be aware of images, feelings, and internal dialogue. For present purposes a crime fantasy (involving rape, murder, or both) was positively coded if the interview or archival data indicated that the daydreaming content included intentional infliction of harm in a sadistic or sexually violent way.

In the case of a serial murderer, the crime scene of the first sexual homicide was examined. The homicide was classified as organized if the crime scene suggested that a semblance of order existed before, during, and after the offense and that this order was aimed at preventing detection (15). The homicide was classified as disorganized if the crime scene was characterized by great disarray, suggesting that the assault had been committed suddenly and with no apparent plan for preventing detection. The crime scene classifications were made by two special agents from the FBI, who used crime scene data only. These data consisted of physical evidence found at the crime scene that were hypothesized to reveal behavioral and personality traits of the murderer. The crime scene may have included the point of abduction, locations where the victim was held, the murder scene, and the final location of the body. Examples of such crime scene data are the use of restraints, manner of death, presence of a weapon, depersonalization of the victim (e.g., rendering the victim unidentifiable through disfigurement), evidence that the crime was staged, and physical evidence (e.g., personal artifacts of the victim or offender).

The planning variable was defined as premeditation. An offense was coded as planned when there was material evidence of a pre-existing strategy to carry out the crime, as reflected by the presence of crime-specific paraphernalia and/or weapons (as opposed to items or weapons of opportunity). Any evidence that the crime had been rehearsed before its execution (e.g., targeting a specific location) would also be considered planning.

The paraphilias were coded as present if there was clear, unambiguous evidence in the archives or from self-reports that the behavior was practiced and that it was not happenstance. The paraphilias were defined in concrete, behavioral terms and examples were provided—for the subject in the case of self-report and for the coders in the case of archival retrieval.

TABLE 2. Prevalence of Violent Fantasies, Paraphilias, and Organized Crime Scenes in Serial and Single Sexual Murderers^a

Characteristic	Serial (N=25)		Single (N=17)		χ^2 (df=1)	p
	N	%	N	%		
Fantasies of rape, murder, or both	19	86	3	23	14.02	0.001
Paraphilias						
Compulsive masturbation	14	70	6	50	1.28	0.26
Indecent exposure	5	25	1	7	1.81	0.19 ^b
Voyeurism	15	75	6	43	3.60	0.06
Fetishism	15	71	4	33	4.54	0.03
Cross-dressing	5	25	0	0	4.38	0.05 ^b
Organized crime scene						
Organized	17	68	4	24	8.00	0.005
Planned	10	42	7	41	—	—

^aSome data were missing for some individuals, so percentages were based on varying numbers of subjects.

^bDerived from Fisher's exact test (one-tailed).

Eight variables were identified in the FBI data base and the Massachusetts Treatment Center data base that were conceptually identical and theoretically meaningful for testing a series of hypotheses regarding these two samples. The two sets of variables were merged to create a new set of dichotomous variables. The dichotomous variables were analyzed with the chi-square statistic. When the expected frequency for a cell was less than 5, the chi-square test was inappropriate and was replaced by Fisher's exact test (19). No subjects were omitted from the analyses because of missing data.

RESULTS

The results are shown in table 2. The a priori hypothesis regarding fantasy was strongly supported ($\chi^2=14.02$, $df=1$, $p<0.001$). Well over three-quarters of the serial group (86%), compared with less than one-quarter of the single group (23%), evidenced sufficiently obtrusive violent fantasies to be noted in the records.

Our hypothesis of a higher prevalence of paraphilias in the group of serial murderers was also supported. There were higher prevalences of all five paraphilias in the serial group than in the single group, and there were significant differences in fetishism ($\chi^2=4.54$, $df=1$, $p<0.03$) and cross-dressing ($\chi^2=4.38$, $df=1$, $p<0.05$).

Our a priori hypothesis regarding the organization or disorganization of the crime scene also was supported ($\chi^2=8.00$, $df=1$, $p<0.005$). Over two-thirds of the serial murderers' first sexual homicides were organized, while three-quarters of the sexual homicides committed by the single murderers were disorganized. There was no difference between groups with respect to the planning of the murder.

DISCUSSION

Evidence from both clinical (10) and empirical (4) studies has underscored the importance of fantasy as a presumptive drive mechanism for sexual sadism and sexual homicide. This study provides support for that general conclusion and for greater specificity in the role of fantasy. That is, violent fantasy was present in 86% of the multiple (or serial) murderers and only 23% of the single murderers, suggesting a possible functional relationship between fantasy and repetitive assaultive behavior. While the precise function of consummated fantasy is speculative, we concur with MacCulloch et al. (10) that once the restraints inhibiting the acting out of the fantasy are no longer present, the individual is likely to engage in a series of progressively more accurate "trial runs" in an attempt to enact the fantasy as it is imagined. Since the trial runs can never precisely match the fantasy, the need to restage the fantasy with a new victim is established. MacCulloch et al. suggested that the shaping of the fantasy and the motivation for consummating the fantasy may be understood in terms of classical conditioning. Abel and Blanchard (14) discussed the role of fantasy in treatment, noting that "repeated pairing of . . . fantasized cues with orgasm results in their acquiring sexually arousing properties." Consistent with this notion is the finding (20) that at least three social learning variables may be important in linking sexual arousal to deviant fantasy: 1) parental modeling of deviant behavior in blatant or attenuated fashion, 2) repeated associations between the modeled deviant behavior and a strong positive affective response from the child, and 3) reinforcement of the child's deviant response. While it is unlikely that the translation of the fantasy into reality conforms precisely to a classical conditioning model, it does appear that the more the fantasy is rehearsed, the more power it acquires and the stronger the association between the fantasy content and sexual arousal. Indeed, the selective reinforcement of deviant fantasies through paired association with masturbation over a protracted period may help to explain not only the power of the fantasies but why they are so refractory to extinction (20).

Since it is commonly accepted that "normal" people often have sexually deviant fantasies (21), merely having a sadistic and/or homicidal fantasy does not mean that the fantasy will be acted out (22). In fact, fantasy may function as a substitute for behavior. Kaplan (23) has argued, for instance, that sadistic fantasies in healthy individuals may serve the purpose of discharging anger. According to Kaplan, sex and aggression are incompatible affects. The fantasy temporarily discharges the anger, thereby permitting the expression of sexual feelings. The critical question regarding the role of fantasy is What are the disinhibitory factors that encourage the translation of symbolic activity (e.g., the paraphilias) or cognitive activity (e.g., fantasies) into reality?

We found in this study that the serial murderers

evidenced a higher frequency of paraphilias than the single murderers. This is entirely consistent with the greater prevalence of violent fantasy in the serial murderers. Not only does paraphilia suggest a preference for fantasy, but the paraphiliac may be seen as something of a fantasy-stimulus collector who seeks out secret experiences to add to his or her private, internal world of fantasy. Thus, acts such as peeping or exhibitionism serve to cultivate new secret experiences, which not only activate fantasy but provide the incentive (or motive) for playing out the fantasy. As Money (24) commented, "The paraphiliac's ideal is to be able to stage his/her erotic fantasy so as to perceive it as an actual experience."

It is interesting that of the five paraphilias we examined, the two with the largest intergroup differences—fetishism and cross-dressing—are also the ones that represent the enactment of some aspect of the fantasy life. Moreover, there is some evidence that fetishism and transvestism are more often associated with sexual aggression than other paraphilias. Wilson and Gosselin (25) studied a large number of fetishists, sadomasochists, transvestites/transsexuals, and normal control subjects and found that 88% of the fetishists also engaged in either sadomasochism or transvestism. More to the point is the study by Langevin et al. (26), who concluded that sadomasochistic fantasies in conjunction with a high degree of force may be premonitory signs of extreme dangerousness, including sexual murder. Langevin and his colleagues noted elsewhere (27) that not only is transvestism associated with other paraphilias but it "may go hand in hand with violent sexuality."

When the paraphilia is sexual homicide, the experience of the act—obtaining the victim, performing ritualistic acts, engaging the victim sexually either before or after death, killing the victim, disposing of the body, eluding detection, and following the police investigation in the media—provides a compelling motive for repetition (5). To the extent to which these components of the crime are contemplated and thought through beforehand, some element of fantasy must be involved. Indeed, evidence of forethought in the planning and/or execution of the crime is highly associated with degree of organization (15). Consistent with our prediction, the percentage of organized murders was almost three times as high in the group of serial murderers as in the single murderers.

On the other hand, the finding of no intergroup difference in planning is entirely inconsistent with our prediction. A scrutiny of the planning variable revealed several problems. The first was a failure to clearly distinguish between the planning of the offense in general and the planning of the actual murder. For the 10 single murderers who came from the Massachusetts Treatment Center, planning referred to the offense. Thus, for a number of single murderers the offense was coded as planned, but the murder itself appeared to have been unplanned (i.e., it resulted from an accident or lethal force used to subdue the victim). In addition,

we were comparing the only murder committed by a single murderer with the first homicide committed by a serial murderer. In the cases of several serial murderers, the evidence for planning became clearer in subsequent homicides. Since those crimes were not considered, the cases were classified as "not planned."

These preliminary findings, based on a small sample of offenders, provide tentative support for the hypothesis that fantasy life may be importantly related to repeated acts of sexual violence. The potential utility of such a finding, if supported by follow-up studies with larger samples, lies primarily in the area of secondary intervention. Greater sensitivity to various behavioral manifestations of "high-risk fantasy" (e.g., certain paraphilias in conjunction with other critical factors, a history of explicit cruelty to animals, the playing out of sadistic fantasies in subviolent, presumably consenting relationships) may increase the accuracy of forecasting subsequent violence. In some cases of homicide investigation, recognizing the importance of fantasy in initiating and staging some murders has facilitated apprehension (15). Even greater than the potential benefits in crime scene investigation may be the contribution to the beleaguered efforts at clinical prediction of dangerousness. Since it is unlikely that violent behavior will decrease markedly, predictive neutrality is not a viable option. Thus, any assistance in identifying potentially homicidal people before they have murdered—or murder again—has enormous practical importance. One crucial task will be to answer the question of what leads an individual to translate a fantasy into reality. Of all those who harbor sadistic fantasies, only a small (unknown) fraction attempt to play out their fantasies. The presence of fantasy alone is a relatively poor harbinger of future conduct. Consequently, it is essential to scrutinize manifest behaviors that increase the probability of enacting fantasies.

REFERENCES

1. Busch KA, Cavanaugh JL: The study of multiple murder: preliminary examination of the interface between epistemology and methodology. *J Interpersonal Violence* 1986; 1:5–23
2. Revitch E: Sex murder and sex aggression. *Med Soc New Jersey* 1957; 54:519–523
3. Swigert VL, Farrell RA, Yoels WC: Sexual homicide: social, psychological, and legal aspects. *Arch Sex Behav* 1976; 5:391–401
4. Ressler RK, Burgess AW, Douglas JE, et al: Sexual killers and their victims: identifying patterns through crime scene analysis. *J Interpersonal Violence* 1986; 1:288–308
5. Burgess AW, Hartman CR, Ressler RK, et al: Sexual homicide: a motivational model. *J Interpersonal Violence* 1986; 1:251–272
6. Douglas JE, Ressler RK, Burgess AW, et al: Criminal profiling from crime scene analysis. *Behavioral Sciences and the Law* 1986; 41:401–421
7. Wolfgang ME, Ferracuti F: *The Subculture of Violence*. Beverly Hills, Calif, Sage Publications, 1967
8. Brittain RP: The sadistic murderer. *Med Sci Law* 1970; 10:198–207
9. Revitch E: Sex murder and the potential sex murderer. *Dis Nerv Syst* 1965; 26:640–648
10. MacCulloch MJ, Snowden PR, Wood PJW, et al: Sadistic fantasy, sadistic behaviour and offending. *Br J Psychiatry* 1983; 143:20–29
11. Abel GG, Barlow DH, Blanchard EB, et al: The components of rapists' sexual arousal. *Arch Gen Psychiatry* 1977; 34:895–903
12. Abel GG, Becker JV, Blanchard EB, et al: Differentiating sexual aggressives with penile measures. *Criminal Justice and Behavior* 1978; 5:315–332
13. Quinsey VL, Chaplin TC: Penile responses to nonsexual violence among rapists. *Criminal Justice and Behavior* 1982; 9: 372–381
14. Abel GG, Blanchard EB: The role of fantasy in the treatment of sexual deviation. *Arch Gen Psychiatry* 1974; 30:467–475
15. Ressler RK, Burgess AW: Violent crime. *FBI Law Enforcement Bull* 1985; 54:18–25
16. Ressler RK, Burgess AW, Douglas JE: *Sexual Homicide: Patterns and Motives*. Lexington, Mass, Lexington Books, 1988
17. Gardner H: *The Mind's New Science*. New York, Basic Books, 1985
18. Singer JL: *Daydreaming*. New York, Random House, 1966
19. Kendall M, Stuart A: *The Advanced Theory of Statistics*, vol 2. New York, Macmillan, 1979
20. Bandura A: *Principles of Behavior Modification*. New York, Holt, Rinehart & Winston, 1969
21. Crepault C, Couture M: Men's erotic fantasies. *Arch Sex Behav* 1980; 9:565–581
22. Schlesinger LB, Revitch E: *Sexual Dynamics of Antisocial Behavior*. Springfield, Ill, Charles C Thomas, 1983
23. Kaplan HS: *Disorders of Sexual Desire*. New York, Simon & Schuster, 1979
24. Money J: *Love and Love Sickness*. Baltimore, Johns Hopkins University Press, 1980
25. Wilson D, Gosselin C: Personality characteristics of fetishists, transvestites and sadomasochists. *Personality and Individual Differences* 1980; 1:289–295
26. Langevin R, Paitich D, Russon AE: Are rapists sexually anomalous, aggressive, or both? in *Erotic Preference, Gender Identity, and Aggression in Men: New Research Studies*. Edited by Langevin R. Hillsdale, NJ, Lawrence Erlbaum Associates, 1985
27. Steiner BW, Sanders RM, Langevin R: Crossdressing, erotic preference, and aggression: a comparison of male transvestites and transsexuals. *Ibid*

Late Luteal Phase Dysphoric Disorder and *DSM-III-R*

Robert L. Spitzer, M.D., Sally K. Severino, M.D.,
Janet B.W. Williams, D.S.W., and Barbara L. Parry, M.D.

Text and diagnostic criteria for a new category, late luteal phase dysphoric disorder, appear in appendix A of DSM-III-R: "Proposed Diagnostic Categories Needing Further Study." The inclusion of this category in the manual was perhaps the most controversial aspect of the revision of DSM-III. In this paper the authors describe the work of the advisory committee that first proposed the category, the rationale for the category's inclusion in the manual, and the many issues that were the focus of heated debates.

(Am J Psychiatry 1989; 146:892-897)

In the last decade, mental health professionals have become increasingly interested in what has generally been referred to as "premenstrual syndrome," or PMS. This has paralleled a growing public interest in the condition and its treatment by a large number of over-the-counter pharmaceutical products.

PMS has no precise definition but has come to refer to a collection of disturbances in mood or physical symptoms that occur regularly and repetitively before menses and remit once menses begins. Psychiatrists and other mental health professionals have made significant contributions to the burgeoning literature in this area, including the description of the syndrome and its differential diagnosis (1-6), the interaction of hormonal and psychological processes (7-13), theories of the etiology of the disorder (14-16), and treatment of the condition (17-21).

PMS has attracted much attention in the mental health field because of the prominence of mood disturbances in most of the women who have menstrually related symptoms sufficiently severe to cause them to seek clinical attention. Yet there is still no accepted definition of PMS. Most mental health professionals have not been informed about recognizing and treating the syndrome. Therefore, many patients have been untreated; others have been treated incorrectly because they were misdiagnosed as having physical problems (e.g., dysmenorrhea) or other psychiatric disorders (e.g., dysthymia, major depression, personality disorder). Thus, many researchers who study PMS-related disorders have believed there is an urgent need for diagnostic criteria to differentiate cases of PMS in which disturbance of mood predominates from cases of PMS with only physical symptoms and from cases of chronic mental disorder that are merely exacerbated premenstrually. It was hoped that such criteria would minimize the clinically inaccurate use of the term "PMS" and the consequent underdiagnosis, overdiagnosis, and misdiagnosis of the syndrome, which have prevented optimal assessment and clinical care.

Acceptable standardized diagnostic criteria are also needed by the research community to enhance generalizability of the findings from research studies. The usefulness of many past studies of PMS has been limited by the lack of rigorously defined criteria for subject selection.

Diagnostic criteria provide mental health professionals with a common language in which they can communicate about a disorder for which they share professional responsibility. Criteria for PMS were also needed to educate psychiatry and other medical specialties and to clarify to the public the spectrum of PMS-related conditions.

Therefore, in June 1985 an advisory committee to the Work Group to Revise *DSM-III* was convened to consider the inclusion in *DSM-III-R* of a category for a subset of PMS conditions in which mood disturbance

Received April 11, 1988; revision received Dec. 20, 1988; accepted Jan. 5, 1989. From the New York State Psychiatric Institute; the Department of Psychiatry, New York Hospital-Cornell Medical Center, Westchester Division, White Plains; and the University of California, San Diego, School of Medicine. Address reprint requests to Dr. Spitzer, New York State Psychiatric Institute, 722 West 168th St., New York, NY 10032.

Copyright © 1989 American Psychiatric Association.

is a predominant symptom. The advisory committee was selected in consultation with staff of the Clinical Research Branch of the National Institute of Mental Health, which cosponsored the meeting. The committee consisted of Dr. Robert L. Spitzer, chairperson of the Work Group to Revise *DSM-III*, Dr. Janet B.W. Williams, a member of the work group, Dr. Harrison Pope, a psychiatrist who has actively participated in revising several of the *DSM-III* categories, and 11 investigators with special expertise in the area: Judith Abplanalp, Ph.D., Susan Blumenthal, M.D., Jean Endicott, Ph.D., Ira Glick, M.D., Jean Hamilton, M.D., Wilma Harrison, M.D., Roger Haskett, M.D., Howard Osofsky, M.D., Ph.D., Barbara Parry, M.D., David Rubinow, M.D., and Sally Severino, M.D. The selection of these experts was made purely on the basis of their having done research in this area, regardless of whether they favored including a PMS-like category in *DSM-III-R*. Although no gynecologist with expertise in this area was included in the group, many of the committee members were in collaborative work with specialists in obstetrics and gynecology. (Drs. Spitzer, Williams, Pope, Haskett, Parry, and Severino constituted a subcommittee that later worked on revisions of the text and criteria for the category.)

THE *DSM-III-R* CATEGORY

The advisory committee first reviewed previous attempts to define PMS. Recognizing that several members might have reservations about the merits of including a version of PMS in *DSM-III-R*, the issue of whether or not to recommend inclusion of the category in *DSM-III-R* was postponed until the committee had first drafted an initial set of criteria for cases of PMS in which mood disturbance was an essential feature. This draft definition would serve as the basis for the discussion about whether or not to include it in the manual.

In developing the diagnostic criteria, an attempt was made to clarify ambiguities in the definition of PMS that have been obstacles to communication among researchers and clinicians. Appendix 1 presents the final criteria that appear in the appendix in *DSM-III-R*.

Criterion A: the phase of the menstrual cycle. This criterion specifies the temporal relationship between the symptoms of the disorder and the menstrual cycle. Note is made of the fact that the disorder can occur in nonmenstruating woman who have intact ovaries (22, 23).

Criterion B: the symptoms of the disorder. This criterion emphasizes that the diagnosis is not given in cases of PMS in which the only symptoms are physical. Ten symptoms are listed; five are required for the diagnosis. At least one of the symptoms must be a mood disturbance: marked affective lability, persistent anger, marked anxiety, or marked depression. Physical symptoms are included but are given less weight than behavioral symptoms.

Criterion C: severity of the disturbance. Many

women experience mildly unpleasant mood changes premenstrually, but the changes are not severe enough to interfere seriously with their work or their usual social activities or relationships. This would not meet criterion C, which requires that the disturbance be severe enough to impair functioning.

Criterion D: differential diagnosis. It is not uncommon for women with other mental disorders, such as mood disorders or anxiety disorders, to experience premenstrual exacerbations of these disorders (24–27). The cause and treatment of premenstrually exacerbated disorders may well be different from those of disturbances that are limited to the premenstrual phase. This criterion indicates that the diagnosis is not given if the symptoms are only an exacerbation of another disorder.

Criterion E: confirmation by daily ratings. Studies have found that for many women who report severe premenstrual symptoms, daily self-ratings indicate that the symptoms are not as severe as initially reported or that the symptoms do not disappear within a few days after the onset of menses (3, 6). In other cases, daily self-ratings document that there is no consistent relationship between the symptoms and the luteal phase. For these reasons, the diagnosis of this disorder is made only provisionally if based on retrospective reports alone. It should be noted that this stringent requirement—having the woman document prospectively the temporal course of the disorder—is unique to this mental disorder.

The committee considered various names for the disorder, believing it important to avoid using the imprecise term “PMS,” which often is used to describe premenstrual disturbances that are limited to physical symptoms. The first name selected by the committee was “premenstrual dysphoric disorder,” which emphasized that the essential symptoms were unpleasant (dysphoric) mood states. Months later, in recognition of the small number of cases that occur in women who are not menstruating, the name was changed to “periluteal phase dysphoric disorder.” The name was later changed once again, when as a result of a dialogue with colleagues from obstetrics and gynecology, it was recognized that, strictly speaking, the symptoms were not “around” (“peri-”) the luteal phase but actually occurred during the late luteal phase. Thus, the final name was “late luteal phase dysphoric disorder.” (Recognizing the difficulty of such a long name, in the rest of this paper we will refer to the disorder as “LLPDD.”)

The advisory committee then discussed the advantages and disadvantages of including this category in *DSM-III-R*. Participating in the discussion as a nonvoting guest was a representative of the American Psychiatric Association (APA) Committee on Women. She presented her committee's many objections to the inclusion of LLPDD in the manual. With the exception of two members of the advisory committee, the committee strongly supported the inclusion of the category in the new classification. We will describe the issues

bearing on the possible inclusion of LLPDD in *DSM-III-R* that were discussed at this meeting and subsequently.

Over the ensuing months controversy mounted regarding the possible inclusion of the category in *DSM-III-R*. In the end, after careful deliberation, the APA Board of Trustees decided to include the category (with two other controversial categories) in an appendix to *DSM-III-R*.

ISSUES IN THE CONTROVERSY

Many nosologic issues and questions about potential harm to women emerged in the debate about the inclusion of LLPDD in *DSM-III-R*. Following are the major objections to including LLPDD and responses to those objections.

Nosologic Issues

Aren't the previous definitions and categorizations of premenstrual tension adequate? Ever since Frank (28) described "premenstrual tension," there have been several attempts to define the disorder (5) and to describe subtypes based on clusters of premenstrual symptoms that covary together (29–33). However, none of these systems has been widely adopted by investigators or clinicians because of an absence of consensus regarding many critical issues, such as baseline severity of symptoms, degree and duration of symptom change, kind of symptoms required (physical or mood), and degree of social or occupational impairment. Therefore, there is a need for a new consensus definition that can be used by both clinicians and researchers.

Is too little known about the disorder to include it in an official classification that is used by both clinicians and researchers? One of the main criticisms of LLPDD is that too little is known about the condition and that what is known is inadequate and inconsistent. Therefore, adding the category to an official classification of mental disorders, with specified criteria, may seem premature and likely to promote a false sense of knowledge that will actually have the effect of discouraging much needed research.

While it is true that little is known about the etiology and treatment of this condition, there is a general consensus about the descriptive features (the symptoms) of the disorder. In this regard, LLPDD is no different from many mental disorders with unquestioned validity. For example, the etiology and treatment are unknown for antisocial personality disorder and hypochondriasis. In fact, because of the substantial data base available for LLPDD, the advisory committee had relatively little difficulty in agreeing on how to define the disorder with specific diagnostic criteria, in contrast to the difficulty in developing criteria for many of the categories that were in *DSM-III* or added to *DSM-III-R*.

Adding LLPDD to *DSM-III-R* facilitates the research that is needed to discover its etiology and effective treatment, as was the experience with many of the

new categories in *DSM-III*. Diagnostic criteria encourage research, as can be seen by the burgeoning of research on affective illness after diagnostic criteria were developed for affective disorders. It is for all of these reasons that the members of the advisory committee, most of whom are active investigators in this area, were so enthusiastic about developing the diagnostic criteria for LLPDD that would be in *DSM-III-R*.

Isn't the condition already classified as a physical disorder? Many of the opponents of the category questioned the need for this category in a classification of mental disorders, arguing that a suitable category already exists as a gynecologic disorder in the *International Classification of Diseases (ICD)*. While it is true that category 625.4, premenstrual tension syndromes, is included in the genitourinary system section of *ICD*, the category has no diagnostic criteria and no definition. Therefore, it is not at all clear precisely what clinical conditions are subsumed by that category.

The central issue here is whether LLPDD, the definition of which requires both a disturbance of mood and functional impairment, should be classified as a physical disorder or as a mental disorder. We believe that LLPDD meets the *DSM-III-R* definition of a mental disorder: "a clinically significant behavioral or psychological syndrome or pattern that occurs in a person and that is associated with present distress (a painful symptom) or disability (impairment in one or more important areas of functioning)." Furthermore, differential diagnosis of LLPDD, which in most cases involves distinguishing it from other mental disorders, requires the special skills of a mental health professional (1).

Despite the logic of these reasons for classifying LLPDD as a mental disorder, many argued that such a classification implies that biological factors are not central to LLPDD and, furthermore, that this suggests the proper treatment of LLPDD must therefore be psychotherapy. In fact, this is no more true of LLPDD than it is of other mental disorders in which biological factors play a central role and for which biological therapy, such as pharmacotherapy, may be indicated.

An issue related to the inclusion of LLPDD as a mental disorder was concern about the effects on insurance reimbursement for the treatment of "PMS." Many women attending PMS clinics feared loss of insurance coverage if their condition were reclassified as a mental disorder. It is hard to know what the effect on third-party reimbursement will be when the diagnosis is the basis for a claim submission, particularly since LLPDD appears only in the appendix of *DSM-III-R* and therefore is not an official *DSM-III-R* category. In any case, such fiscal considerations should not be the basis for excluding the category from a classification primarily concerned with clinical and scientific issues.

Since all women experience some premenstrual changes, how can LLPDD be considered a disorder? Some of the opponents of LLPDD argued that premenstrual changes in women are universal and therefore LLPDD is only an arbitrary selection of the extreme

expression of a normal phenomenon. The problem with this argument is that the same argument could be made for many well-established diagnoses. For example, one extreme end of the distribution of intelligence in the population is recognized as mental retardation, extreme forms of sadness or grief are recognized as depressive disorders, and extreme concern with body weight, size, or shape is recognized as an eating disorder. As with LLPDD and these other diagnoses, care must be given to defining them so that the boundary between normality and pathology maximizes the validity (utility) of the category for research and clinical care. In the case of LLPDD, the diagnostic criteria assure that only a relatively small portion of women with premenstrual symptoms will qualify for the diagnosis.

Since there is no objective measure for the LLPDD diagnostic criterion of functional impairment, how valid can the diagnosis be? It is true that in making the diagnosis of LLPDD, the clinician, in the absence of other confirming data (e.g., from a spouse), must rely solely on the subject's assessment of whether the symptoms are so severe that they "seriously interfere with work or with usual social activities or relationships with others." However, the same problem exists in making other diagnoses. For example, the diagnosis of obsessive-compulsive disorder or of simple phobia may also require a clinical judgment that the symptoms significantly interfere with the person's functioning.

Doesn't "late luteal phase dysphoric disorder" imply a theory that is as yet unproven, that something is biologically wrong with the menstrual cycle? This is a subtle but interesting argument. As yet, research has not revealed any biological abnormality, such as endocrine disturbances, in women with severe premenstrual symptoms. Therefore, LLPDD may be a disorder not of the menstrual cycle itself but associated with the menstrual cycle. Another aspect of this argument is that the name of the disorder, because it implies biological causality, will bias future research away from the exploration of other etiologic factors, such as social and psychological factors. For example, Parlee (34) has suggested that stereotyped cultural beliefs about menstruation contribute to the development of premenstrual symptoms in certain women.

Like almost all of the other names in *DSM-III-R*, "late luteal phase dysphoric disorder" is descriptive and does not imply any particular theory about etiology. We certainly hope that all potentially fruitful approaches to etiology will be explored, including the role of psychological and social factors.

Isn't gender bias inherent in the fact that, by definition, LLPDD can only be diagnosed in women? This is simply not true. Many mental disorders are differentially prevalent according to gender. Just as many diagnoses in *DSM-III* and *DSM-III-R* are more common in women (e.g., depressive disorders), many are far more common in men (e.g., antisocial personality disorder, psychoactive substance use disorders) and some are hardly ever seen in women (e.g., the paraphilias). One *DSM-III-R* disorder, premature ejaculation, by

definition, can only be diagnosed in men, and there is no analogous category in women.

Social Issues

In the debate about LLPDD the social issues all focused on the potential harm to women that could result from the inclusion of the category in *DSM-III-R*.

Will the inclusion of LLPDD in DSM-III-R reinforce primitive myths about women's "raging hormones" and their special vulnerability? There are two separate issues here. The myth of women's "raging hormones" implies that all women are cyclically unstable and defective. However, the recognition that some women have a cyclic disorder associated with the menstrual cycle certainly does not imply that all women who menstruate are disordered. In fact, it suggests the opposite: that the majority of women do not have mood disturbances in relation to the menstrual cycle. The second issue is that of vulnerability. Just as men are vulnerable to developing certain disorders, so too are women. It is not "antiwomen" to recognize LLPDD any more than it is "antimen" to recognize the many disorders that are more common in men.

Won't LLPDD stigmatize women in the workplace and discourage them from seeking clinical care? It is true that an employer might be reluctant to hire a woman who acknowledges that she suffers from LLPDD. However, an employer might well be reluctant to hire a woman who acknowledges any mental or physical disorder that could impair her job functioning. Certainly, an employer should be even more wary of hiring a man with antisocial personality disorder or with a psychoactive substance use disorder than a woman with LLPDD. The solution to the problem of unfair discrimination in the workplace against individuals with mental disorders is certainly not to pretend that the disorders do not exist.

It is true that many women with LLPDD are uncomfortable with the idea that they suffer from a mental disorder, and some of these women might be reluctant to seek help if they knew that the disorder was regarded as such. However, large numbers of women throughout the country seek help from the many clinics in departments of psychiatry that specialize in the study and treatment of this condition. This indicates that the stigma of mental illness does not discourage at least many of them from seeking clinical care.

Since the diagnosis of LLPDD requires impaired functioning, could it be used against a woman seeking child custody in a divorce case? The answer is yes, but the legal issue is the same as for any mental disorder, such as a depressive disorder. In the case of LLPDD, it would have to be demonstrated that the mother's episodic impaired functioning resulted in harm to her child. However, as Benson has noted, "Although recent publicity about PMS has aggravated fears among women that PMS will justify assaults on them, cause them to lose custody of their children and otherwise disadvantage them in the area of domestic relations,

the case law has not reflected this. Regardless of PMS, an inquiry into the fitness or behavior of a parent or partner is frequently relevant" (S. Benson, Esq., "Premenstrual Syndrome as a Criminal Defense," presented at the Association of Trial Lawyers of America 1986 annual conference, New York, July 15, 1986). If LLPDD were recognized as an official mental disorder, issues related to its use would be no different from the issues surrounding the use of other mental disorders in the judicial system.

Since PMS has already been successfully used as an insanity defense in a murder case in England, could LLPDD be used in this way in this country in the future? Under current laws in most of the states, the presence of a mental disorder can be used to support an insanity defense only when there is evidence that the individual is unable to appreciate the consequences of his or her actions. This generally requires the demonstration that the individual suffers from a psychotic disorder. Because LLPDD rarely involves psychotic behavior, it is unlikely that it would often be used successfully as a psychiatric defense in a criminal case in this country. In the rare case in which LLPDD was associated with psychotic symptoms, it would be up to the jury to decide if the presence of the disorder was relevant to an insanity defense or whether the presence of the disorder should be a mitigating factor in sentencing (35, 36).

Given the potential for stigma, what is the value of including the category in DSM-III-R when there is no known effective treatment and no known cause for the disorder? It is true that research has not yet reached consensus about a particular treatment that has proven effective in replicated double-blind controlled studies (18, 37). However, as noted before, there are many other mental disorders (as well as physical disorders) included in our classification system for which proven effective treatments have yet to be developed. Researchers need a standard definition in order to evaluate various treatments and to investigate the causes of the disorder.

DISCUSSION

The debate about including LLPDD in *DSM-III-R* had many benefits. The interest in the category assured that the diagnostic criteria were developed with great care and attention to the problems of differential diagnosis. The issue of whether the condition should be classified as a mental or a physical disorder demonstrated the common misunderstanding many have about the meaning of the concept of "mental disorder": to many, "mental disorder" implies only psychological causation and psychological treatment. Finally, the concern with the category's stigmatizing effect on women demonstrates a pervasive fear in our culture that the gains women have made toward equality in recent years can be easily undermined by recognition of women's special health needs.

Large numbers of women with LLPDD are being treated with medications of unknown efficacy. There is therefore an urgent need for controlled double-blind treatment studies. Future research should, however, not neglect psychological issues, such as the effect of the symptoms on family functioning (marital relations and relations with children) and the role of the family, in some cases, of initiating or sustaining the disorder. We anticipate that research on these and other issues, such as etiology, will be facilitated by having the category defined and described in *DSM-III-R*. We believe this will result in better health care for women and reduce the suffering of women with this disorder.

The developers of *DSM-IV* will have to decide whether there is sufficient evidence to justify the inclusion of this category in the next revision of our diagnostic manual. If it is included, we suggest a less cumbersome name: "luteal dysphoric disorder." Although the terms "early" and "phase" have the advantage of precision, their absence should cause no confusion as to what is meant by the diagnostic term.

REFERENCES

1. DeJong R, Rubinow DR, Roy-Byrne P, et al: Premenstrual mood disorder and psychiatric illness. *Am J Psychiatry* 1985; 142:1359-1361
2. Endicott J, Halbreich U, Schacht S, et al: Premenstrual changes and affective disorders. *Psychosom Med* 1982; 43:519-529
3. Endicott J, Halbreich U: Retrospective reports of premenstrual changes: factors affecting confirmation by daily ratings. *Psychopharmacol Bull* 1982; 18:109-112
4. Halbreich U, Endicott J, Nee J: The diversity of premenstrual changes as reflected in the premenstrual evaluation form. *Acta Psychiatr Scand* 1982; 65:46-65
5. Osofsky HJ, Blumenthal SJ (eds): *Premenstrual Syndrome: Current Findings and Future Directions*. Washington, DC, American Psychiatric Press, 1985
6. Rubinow DR, Roy-Byrne P, Hoban MC: Prospective assessment of menstrually related mood disorders. *Am J Psychiatry* 1984; 141:684-686
7. Benedek T, Rubenstein BB: The correlations between ovarian activity and psychodynamic processes, I: the ovulatory phase. *Psychosom Med* 1939; 1:245-270
8. Benedek T, Rubenstein BB: The correlations between ovarian activity and psychodynamic processes, II: the menstrual phase. *Psychosom Med* 1939; 1:461-485
9. Glick ID, Bennett S: Psychiatric effects of progesterone and oral contraceptives, in *Psychiatric Complications of Medical Drugs*. Edited by Shader R. New York, Raven Press, 1972
10. Hamilton JA, Aloï J, Mucciardi B, et al: Human plasma β -endorphin through the menstrual cycle. *Psychopharmacol Bull* 1983; 19:586-587
11. Rausch JL, Janowsky DS, Risch SC, et al: Hormonal and neurotransmitter hypotheses of premenstrual tension. *Psychopharmacol Bull* 1982; 18:26-34
12. Severino SK, Bucci W, Creelman ML: Cyclical changes in emotional information processing in sleep and dreams. *J Am Acad Psychoanal* (in press)
13. Halbreich U, Endicott J: Possible involvement of endorphin withdrawal or imbalance in specific premenstrual syndromes and postpartum depression. *Med Hypotheses* 1981; 7:1045-1058
14. Rausch JL, Janowsky DL: *Premenstrual tension: etiology, in Behavior and the Menstrual Cycle*. Edited by Friedman RC. New York, Marcel Dekker, 1982
15. Roy-Byrne PP, Rubinow DR, Hoban MC, et al: TSH and pro-

- lactin responses to TRH in patients with premenstrual syndrome. *Am J Psychiatry* 1987; 144:480-484
16. Steiner M, Haskett RF, Carroll BJ, et al: Plasma prolactin and severe premenstrual tension. *Psychoneuroendocrinology* 1984; 9:29-35
 17. Glick RD, Steward D: A new drug treatment for premenstrual exacerbation of schizophrenia. *Compr Psychiatry* 1980; 21: 281-287
 18. Harrison W, Sharpe L, Endicott J: Treatment of premenstrual symptoms. *Gen Hospital Psychiatry* 1985; 7:54-65
 19. Parry BL, Rosenthal NE, Tamarkin L, et al: Treatment of a patient with seasonal premenstrual syndrome. *Am J Psychiatry* 1987; 144:762-766
 20. Steiner M, Carroll BJ: The psychobiology of premenstrual dysphoria: review of theories and treatment. *Psychoneuroendocrinology* 1977; 2:321-335
 21. Steiner M, Haskett RF, Osmun JN, et al: Treatment of premenstrual tension with lithium carbonate. *Acta Psychiatr Scand* 1980; 61:96-102
 22. Backstrom CT, Boyle HJ, Baird DT: Persistence of symptoms of premenstrual tension in hysterectomized women. *Br J Obstet Gynaecol* 1981; 88:530-536
 23. Reid RL: Premenstrual tension, in *Current Problems in Obstetrics, Gynecology and Fertility*. Edited by Leventhal JM, Hoffman JJ, Keith LG, et al. Chicago, Year Book Medical Publishers, 1985
 24. Gladis MM, Walsh BT: Premenstrual exacerbation of binge eating in bulimia. *Am J Psychiatry* 1987; 144:1592-1595
 25. Glick ID, Steward D: A new drug treatment for premenstrual exacerbation of schizophrenia. *Compr Psychiatry* 1980; 21: 281-287
 26. Roy-Byrne PP, Hoban MC, Rubinow DR: The relationship of menstrually related mood disorders to psychiatric disorders, in *Clinical Obstetrics and Gynecology*. Edited by Johnson SR. Hagerstown, Md, JB Lippincott, 1987
 27. Williams EY, Weekes LR: Premenstrual tension associated with psychotic episodes. *J Nerv Ment Dis* 1952; 116:231-239
 28. Frank RT: The hormonal basis of premenstrual tension. *Arch Neurol Psychiatry* 1931; 26:1053-1057
 29. Moos RH, Kopell BS, Melges FT, et al: Fluctuations in symptoms and moods during the menstrual cycle. *J Psychosom Res* 1969; 13:37-44
 30. Haskett RF, Steiner M, Osmun JN, et al: Severe premenstrual tension: delineation of the syndrome. *Biol Psychiatry* 1980; 15: 121-139
 31. Hargrove JT, Abraham GE: The ubiquitousness of premenstrual tension in gynecologic practice. *J Reprod Med* 1983; 28: 435-437
 32. Abraham GE, Rumley RE: Role of nutrition in managing the premenstrual tension syndromes. *J Reprod Med* 1987; 32:405-421
 33. Halbreich U, Endicott J: Classification of premenstrual syndrome, in *Behavior and the Menstrual Cycle*. Edited by Friedman RC. New York, Marcel Dekker, 1982
 34. Parlee MB: Stereotypic beliefs about menstruation: a methodological note on the Moos Menstrual Distress Questionnaire and some new data. *Psychosom Med* 1974; 36:29-40
 35. Dalton K: Menstruation and crime. *Br Med J* 1961; 2:1752-1753
 36. Benedek E: Premenstrual syndrome: a new defense? in *The Psychiatric Implications of Menstruation*. Edited by Gold JH. Washington, DC, American Psychiatric Press, 1985
 37. Muse KN, Cetel NS, Futterman LA, et al: Premenstrual syndrome: effects of "medical ovariectomy." *N Engl J Med* 1984; 311:1345-1349

APPENDIX 1. Diagnostic Criteria for Late Luteal Phase Dysphoric Disorder

A. In most menstrual cycles during the past year, symptoms in B occurred during the last week of the luteal phase and remitted within a few days after onset of the follicular phase. In menstruating females, these phases correspond to the week before, and a few days after, the onset of menses. (In nonmenstruating females who have had a hysterectomy, the timing of luteal and follicular phases may require measurement of circulating reproductive hormones.)

B. At least five of the following symptoms have been present for most of the time during each symptomatic late luteal phase, at least one of the symptoms being either (1), (2), (3), or (4):

- (1) marked affective lability, e.g., feeling suddenly sad, tearful, irritable, or angry
- (2) persistent and marked anger or irritability
- (3) marked anxiety, tension, feelings of being "keyed up," or "on edge"
- (4) markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
- (5) decreased interest in usual activities, e.g., work, friends, hobbies
- (6) easy fatigability or marked lack of energy
- (7) subjective sense of difficulty in concentrating
- (8) marked change in appetite, overeating, or specific food cravings
- (9) hypersomnia or insomnia
- (10) other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," weight gain

C. The disturbance seriously interferes with work or with usual social activities or relationships with others.

D. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as Major Depression, Panic Disorder, Dysthymia, or a Personality Disorder (although it may be superimposed on any of these disorders).

E. Criteria A, B, C, and D are confirmed by prospective daily self-ratings during at least two symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

Effect of a Psychiatric Liaison Program on Consultation Rates and on Detection of Minor Psychiatric Disorders in Cancer Patients

Cheryl F. McCartney, M.D., Patricia Cahill, M.D., David B. Larson, M.D., M.S.P.H., John S. Lyons, Ph.D., Cicilia Y. Wada, Ph.D., and Harold Alan Pincus, M.D.

Because only 2% of the 47% of cancer patients with psychiatric disorders receive psychiatric consultations, the authors investigated the impact of a psychiatric liaison program on improving consultation rates on a gynecologic oncology unit. Consultation rates for gynecologic cancer patients before and after introduction of the program were compared to rates from other cancer patients in the same hospital during the same 7-year period. Rates for the gynecologic patients were higher after the program (9%) than before (4%), as were rates for follow-up consultations, and the detection of minor DSM-III disorders improved. The authors conclude that liaison improves access to psychiatric treatments that often enhance the quality of life for seriously ill patients.

(Am J Psychiatry 1989; 146:898-901)

Although 47% of cancer patients suffer from psychiatric disorders (1), the reported request rate for psychiatric consultations for this population is only about 2% of annual cancer admissions (2). Similarly, of the 30%–60% of medically ill hospitalized patients estimated to have psychiatric comorbidities, only 1%–

3% receive psychiatric consultations (3). Since the majority of psychiatric diagnoses in cancer patients are adjustment disorders that are responsive to brief therapies (4) and since improved quality of life, not cure, is the only realistic goal for about 50% of cancer patients (5, 6), it is important to achieve higher psychiatric consultation rates for these patients.

The inability of primary care physicians to identify psychiatric problems (7–9) and their belief that psychiatric intervention is not helpful (9) have been cited as the reasons for low consultation rates in medically ill patients. Psychiatric consultation-liaison intervention programs attempt to improve physicians' recognition of emotional problems and trust in psychiatry's effectiveness by providing education, screening of patients to detect psychiatric disorders, and therapeutic services to patients with psychiatric disorders (10). Efforts to train primary care physicians to care for patients with psychiatric disorders have yielded disappointing results. Thus, in their review of evaluative studies in consultation-liaison psychiatry, McKegney and Beckhardt (11) concluded that a realistic goal for such interventions would be the consultees' identification and referral of medically ill patients with psychiatric disorders (11).

Although several descriptive reports have demonstrated the benefits of liaison (11), only one study (12) quantified the increase in consultation that is associated with liaison. However, the general applicability of the findings is limited because the authors compared the impact of "active" liaison to an already existing liaison program, the intervention period was short (6 months), the study sample was small and had heterogeneous medical problems, and no statistical tests were performed on the frequency data.

Our study improves on the methods of Torem et al.

Presented at the 141st annual meeting of the American Psychiatric Association, Montreal, Que., Canada, May 7–13, 1988. Received Sept. 28, 1987; revision received Jan. 11, 1989; accepted Feb. 2, 1989. From the Department of Psychiatry, University of North Carolina School of Medicine. Address reprint requests to Dr. McCartney, University of North Carolina School of Medicine, CB 7160, Chapel Hill, NC 27599.

Supported by National Cancer Institute grant R25-17973.

The authors thank Sandra Stinnett, M.S., and Angela Poole for their contributions.

Copyright © 1989 American Psychiatric Association.

(12) in that we evaluated the impact of a new psychiatric liaison program on consultation rates. Our intervention period was longer (3 years), the patient sample was homogeneous (women with gynecologic cancer), and outcome was compared to two relevant comparison groups without liaison: women with gynecologic cancer in the 4 years before the liaison program was introduced and people with all other cancers in the same hospital during the 7-year study period. We also examined the rates of minor psychiatric diagnoses and of follow-up consultations during subsequent admissions in these patient groups.

METHOD

The patients in this 7-year study received care in a university hospital's referral oncology program. Two time periods were examined: 1) the 4 years before psychiatric liaison intervention with the gynecologic oncology service, and 2) the first three years after the liaison program was introduced. The 1,798 gynecologic cancer patients served during the time period that the liaison program was in effect composed the experimental group. The 1,092 gynecologic cancer patients served during the time period before the liaison program were one comparison group. To control for any effects of changing hospital or reimbursement policies between the time periods a second comparison group, all other cancer patients in the same hospital during each time period ($N=8,823$), was studied. Each cancer group-time period subsample was classified according to whether psychiatric consultation had or had not been received.

Physician residents serving monthly rotations on oncology services were the consultees. The consultations for the comparison groups were distributed among all psychiatric consultation faculty and their residents. For the experimental group (i.e., the gynecologic cancer patients served during the liaison program), all consultations were performed by a psychiatrist (C.F.M.) (and/or two of her advanced residents doing year-long electives) who had developed a working relationship with the permanent attending staff and rotating gynecology residents. The consultants had learned the presentation, treatment, and prognoses for the types of gynecologic cancer of the patients on the oncology service and attended team conferences in which all patients' psychosocial statuses were discussed. These psychiatrists performed psychiatric evaluations on request, supervised oncologists' implementation of psychiatric recommendations (e.g., counseling, medication), and provided brief psychotherapy (individual, marital, and family).

We obtained demographic information about all patients served during the 7-year period from the Computerized Cancer Data Base for North Carolina Memorial Hospital and the Lineberger Cancer Research Center. For patients who had psychiatric consultations, hospital charts were the source of data about

age, race, marital status, economic status, site and extent of cancer at the time of first diagnosis and at consultation, duration of life from consultation until death (a measure of severity of illness), reason for consultation, and psychiatric diagnosis.

Consultation rates were defined as the number of patients in a category who had consultations divided by the total number in that category who had been seen at the hospital multiplied by 100. *DSM-III* diagnoses were classified as major (organic mental disorder, schizophrenia, major depression, paranoia, alcohol/substance abuse, personality disorder, anxiety disorder, psychosis, and mental retardation) or minor (adjustment disorder, life circumstance problem, psychological factors affecting physical condition). Because 15% of the patients who had consultations in each time period received no final psychiatric diagnosis or had no psychiatric disorder, they were excluded from this calculation. Then, the percent of the remaining patients with consultations that resulted in minor diagnoses was calculated. Follow-up consultations were those ordered for patients who had had initial consultations in previous admissions. A follow-up consultation percent was calculated by dividing the number of patients who received follow-up consultations by the total number who had received consultations initially.

The chi-square statistic was used to test the significance of the difference in the consultation rates between cancer groups in each of the two time periods and differences between time periods for each cancer group. To address the primary question of whether the liaison intervention was associated with higher consultation rates, we computed the difference between the consultation rate before and the consultation rate after introduction of the liaison program for each cancer group. Then, the significance of the difference between these differences was tested by using a Z test of differences in proportions (13). For consistency, these results are reported as chi-square statistics. A similar analysis was used to assess the effect of the liaison program on the consultation rate for those with minor psychiatric diagnoses and on the follow-up consultation rate.

RESULTS

Within each patient group (gynecologic cancer and other types of cancer) from which consultations were drawn, there were no differences in age, race, or marital status between time periods (before and after the introduction of the liaison program). However, the other cancer group was significantly older than the gynecologic cancer group; 72% and 58%, respectively, were older than 50 years in both time periods (before: $\chi^2=81.4$, $df=1$, $p<0.001$; after: $\chi^2=176.7$, $df=1$, $p<0.001$). The other cancer group also had a significantly higher percent of white patients than the gynecologic group (68% and 59%, respectively, in

TABLE 1. Consultation Rates of Cancer Patients Before and After Introduction of a Psychiatric Liaison Program to a Gynecologic Oncology Service

Group and Time Period	Patients	Patients With Consultations						
		Initial Consultation		Follow-Up Consultations		With DSM-III Diagnosis		
		N	%	N	%	Any	Minor	
Gynecologic cancer	2,890	204	7.1	41	20.1	173	101	58.4
Before liaison program	1,092	45	4.1 ^{a,b}	6	13.3	40	20	50.0
After liaison program	1,798	159	8.8 ^{a,c}	35	22.0 ^d	133	81	60.9 ^e
Difference	—	—	4.7 ^f	—	8.7	—	—	10.9
Other types of cancer (no liaison program)	8,823	184	2.1	22	12.0	153	66	43.1
Before gynecologic liaison program	3,209	72	2.2 ^b	8	11.1	59	23	39.0
After gynecologic liaison program	5,614	112	2.0 ^c	14	12.5 ^d	94	43	45.7 ^e
Difference	—	—	-0.2 ^f	—	1.4	—	—	6.8

^aSignificant difference between time periods for gynecologic group ($\chi^2=23.09$, $df=1$, $p<0.001$).

^bSignificant difference between cancer groups before the program ($\chi^2=10.85$, $df=1$, $p<0.001$).

^cSignificant difference between cancer groups after the program ($\chi^2=181.37$, $df=1$, $p<0.001$).

^dSignificant difference between cancer groups after the program ($\chi^2=4.02$, $df=1$, $p=0.05$).

^eSignificant difference between cancer groups after the program ($\chi^2=5.11$, $df=1$, $p=0.02$).

^fSignificant overall difference between cancer groups ($\chi^2=26.94$, $df=1$, $p<0.001$).

both time periods) (before: $\chi^2=28.1$, $df=1$, $p<0.001$; after: $\chi^2=71.9$, $df=1$, $p<0.001$). The proportion of patients who were married did not differ significantly between the other cancer group and the gynecologic cancer group before the liaison program (59% and 56%) ($\chi^2=3.1$, $df=1$, $p<0.08$) but was significantly different after the liaison program (55% and 60%) ($\chi^2=11.5$, $df=1$, $p<0.001$). There was no difference in socioeconomic status between time periods for the gynecologic cancer patients who had consultations, but these were the only patients for whom socioeconomic status could be ascertained. Consultation patients in all subgroups had more advanced disease than would be expected in a general population of cancer patients (6). Extent of disease was beyond local invasion in about 75% of all the cancer patients with consultations. Among the patients who had consultations, 47% with gynecologic cancer and 38% with other types of cancer lived less than 1 month after the initial consultation. By 2 months after the initial consultation, about 50% of all the cancer patients had died, and by 6 months about 65% had died.

As indicated in table 1, the initial consultation rate was significantly higher in the gynecologic group after the liaison program than before the program, but there was no change in rates between time periods for the other cancer group. In both time periods, the initial consultation rate was higher in the gynecologic group than in the other cancer group. These results suggest that a liaison program positively influences the rate of consultations requested.

To assess the effect of the liaison program on the detection of minor psychiatric diagnoses, the consultation patients who had been given DSM-III diagnoses were analyzed (table 1). There was no difference in

distribution of major and minor diagnoses between cancer groups who had consultations before the liaison program. Among those with consultations after the liaison program, a higher percent of gynecologic patients than other cancer patients received minor diagnoses. The percent of patients with consultations who received minor diagnoses was not significantly higher after the program than before the program in either group. There was no significant difference between the groups with respect to these differences over time.

Before the liaison program, there was no difference in the follow-up consultation rate between the cancer groups. After the program, a significantly higher percent of patients in the gynecologic cancer group than in the other cancer group had more than one consultation. The follow-up consultation rate was not significantly higher after the liaison program than before the program in either group, and the difference between the consultation rates from before to after the program also was not significantly different between the groups. These data are also presented in table 1.

DISCUSSION

We found that consultation rates were significantly higher after the introduction of a psychiatric liaison program to a gynecologic oncology service. The liaison program was also associated with a higher percent of consultations for minor psychiatric diagnoses and with a higher rate of follow-up consultations ordered on subsequent hospital admissions among gynecologic patients. The differences with respect to minor psychiatric diagnoses and follow-up consultations were attenuated by large standard errors that accompanied

the measured differences in proportions from before the program to after the program between the two cancer groups. With a larger sample of consultation patients, these differences might be significant.

Simple treatments that are often effective for psychiatric disorders in cancer patients would not be available to such patients without detection of the problems and requests for consultation by their oncologists. Thus, our finding of a higher consultation rate after the introduction of a liaison program, given the reported prevalence of psychiatric disorders in cancer patients, suggests that liaison contributes to improved clinical outcomes for cancer patients. Symptoms can usually be eliminated or reduced to a tolerable level by brief supportive psychotherapy based on a crisis intervention model and psychotropic medication (4, 14). Massie and Holland (4) reported that only one to four visits were necessary for 58% of their oncology consultation patients.

The finding that the majority of consultations were for patients nearing death confirms other reports that oncologists are most likely to request psychiatric intervention for patients with advanced cancer. Massie and Holland (4) reported that 77% of their consultations were for patients with stage III or IV disease. In addition to evidence that patients with the poorest cancer prognoses have the most severe psychiatric disorders (15, 16), oncologists' beliefs about emotional needs in cancer patients may also influence their requests for consultations. Although oncologists may believe that emotional distress is a normal and understandable reaction to cancer, which will remit if the cancer is cured, they may select patients for consultations because of perceived poor prognoses (17). When no further curative treatments remain, oncologists may be more willing to offer psychiatric intervention to provide comfort and to help patients cope with death.

A prevalence study (1) of psychiatric diagnoses in cancer patients showed that 68% of those with psychiatric disorders have adjustment disorders. Some patients with these minor diagnoses may not be referred because oncologists may find these disorders more difficult to detect than the more intense and obvious major psychiatric disorders. Other reasons for nonreferral could be that minor disorders are detected but felt not to require psychiatric assistance or that patients are unwilling to see a psychiatrist. The first hypothesis is supported by 1) the finding of Derogatis et al. (7) that oncologists rated cancer patients lower on dimensions of depression than the patients rated themselves and 2) our finding that after the liaison program there was a higher percent of gynecologic patients who received consultations and who were given minor psychiatric diagnoses. Thus, the results suggest that the liaison program helped the oncologists to detect the more subtle disorders. The higher rate of follow-up consultations associated with liaison may reflect the oncologists'

direct observations of the beneficial contribution of psychiatry to patient care.

Specific knowledge of the psychiatric and oncologic needs of cancer patients combined with an ongoing interpersonal relationship with the gynecologic oncology unit staff were the features that distinguished the psychiatrists providing consultation to the gynecologic cancer group after the introduction of a liaison program from those providing consultation to the groups that did not have the benefit of such a program. The initial and follow-up consultation rates suggest that the liaison program had a beneficial influence on the oncologists' appreciation of the need for psychiatric intervention and on their ability to detect more subtle (minor) psychiatric disorders.

REFERENCES

1. Derogatis LR, Morrow GR, Fetting J, et al: The prevalence of psychiatric disorders among cancer patients. *JAMA* 1983; 249: 751-757
2. Levine PM, Silberfarb PM, Lipowski ZJ: Mental disorders in cancer patients: a study of 100 psychiatric referrals. *Cancer* 1978; 42:1385-1391
3. Wallen J, Pincus HA, Goldman HH, et al: Psychiatric consultations in short term general hospitals. *Arch Gen Psychiatry* 1987; 44:163-168
4. Massie MJ, Holland JC: Consultation and liaison issues in cancer care. *Psychiatr Med* 1987; 5:343-359
5. McCartney CF, Larson DB: Quality of life in patients with gynecologic cancer. *Cancer* 1987; 60(8, Suppl):2129-2136
6. 1988 Cancer Facts and Figures. New York, American Cancer Society, 1988
7. Derogatis LR, Abeloff MD, McBeth CD: Cancer patients and their physicians in the perception of psychological symptoms. *Psychosomatics* 1976; 17:197-201
8. Schubert DSP, Gabinet L, Friedson W, et al: The identification of psychiatric morbidity by internists and subsequent selection for psychiatric referral. *Int J Psychiatry Med* 1978/1979; 9: 317-327
9. Steinberg H, Torem M, Saravay SM: An analysis of physician resistance to psychiatric consultations. *Arch Gen Psychiatry* 1980; 37:1007-1012
10. Mohl PC: What model of liaison psychiatry meets whose needs? *Gen Hosp Psychiatry* 1983; 5:213-215
11. McKegney FP, Beckhardt RM: Evaluative research in consultation-liaison psychiatry. *Gen Hosp Psychiatry* 1982; 4:197-218
12. Torem M, Saravay SM, Steinberg H: Psychiatric liaison: benefits of an "active" approach. *Psychosomatics* 1979; 20:598-611
13. Fleiss JL: *Statistical Methods for Rates and Proportions*, 2nd ed. New York, John Wiley & Sons, 1981, p 108
14. Evans DL, McCartney CF, Haggerty JJ, et al: Treatment of depression in cancer patients is associated with better life adaptation: a pilot study. *Psychosom Med* 1988; 50:72-76
15. Cassileth BR, Lusk EJ, Strouse TB, et al: A psychological analysis of cancer patients and their next-of-kin. *Cancer* 1985; 55: 72-76
16. Cain EN, Kohorn EI, Quinlan DM, et al: Psychosocial reaction to the diagnosis of gynecologic cancer. *Obstet Gynecol* 1983; 62:635-641
17. McCartney CF, Larson DB, Wada CY, et al: Effect of psychiatric liaison on consultation rates and reasons for consult in gynecologic oncology. *J Psychosomatic Obstetrics and Gynecology* 1986; 5:253-261

Informed Consent and Tardive Dyskinesia

Irwin Kleinman, M.D., F.R.C.P.(C), Debbie Schachter, M.Sc., M.D., F.R.C.P.(C),
and Endre Koritar, M.D., F.R.C.P.(C)

To determine whether a formalized informing process transmitted knowledge concerning the risks and benefits of neuroleptic medication, particularly the risk of tardive dyskinesia, to stable schizophrenic outpatients, the authors administered a multiple-choice questionnaire to 21 patients who were read a standardized information form and 27 patients who were not. The mean scores for the informed patients were significantly higher, and the differences between the two groups remained significant at 6-month follow-up. The information process had no adverse effects on frequency of psychiatric admission, noncompliance with medication, or the need for increased antipsychotic medication.

(Am J Psychiatry 1989; 146:902-904)

Maintenance treatment with neuroleptic drugs, the most effective treatment for preventing relapse in schizophrenic patients (1, 2), is complicated by the risk of tardive dyskinesia, an irreversible movement disorder that affects 20%–25% of patients who take maintenance neuroleptics (1, 3, 4). Obtaining informed consent for treatment is a generally accepted practice in medicine. Because of the high prevalence and potential irreversibility of tardive dyskinesia, informed consent is particularly important for patients receiving long-term neuroleptic therapy. To be adequately informed, a patient must understand the nature, benefits, and risks of the proposed treatment as well as the benefits and risks of the alternative choices, including no treatment (5).

Several investigators have tried to determine patients' knowledge about neuroleptic medication. Geller (6) surveyed the population of a state hospital and found that only 8% of patients correctly indicated the name of at least one medication they were taking, its dose, schedule, and intended effect. This study,

however, did not assess patients' understanding of side effects or risks of medication. Soskis (7), comparing schizophrenic inpatients with a matched group of medical inpatients, found that medical inpatients were better informed about positive aspects of medication, such as name and dose, and schizophrenic patients were significantly better informed about side effects and risks; however, it was sufficient to be able to name one risk of medication to be considered informed about the risks. These studies estimate prevalence of knowledge in populations, but they do not state whether the patients had been informed about neuroleptic medication. It is unclear whether these patients' lack of knowledge reflects their lack of information or their inability to comprehend and retain information.

Three studies bridge this gap by evaluating patients' knowledge following an informing process. Grossman and Summers (8) informed 20 schizophrenic outpatients about psychotropic medication. They found that the average subject only understood about half the material presented. Irwin et al. (9) found that objective ratings did not support the perceptions of most of the acutely psychotic patients that they had understood the information presented. A study by Munetz and Roth (10) compared a written approach and an oral approach to inform 25 schizophrenic outpatients with tardive dyskinesia about the risks and benefits of neuroleptic medication. Both groups showed significant increases in knowledge immediately after the informing process, but only the oral presentation group retained the new knowledge at 2-month follow-up. Munetz and Roth also found that younger patients (those younger than 50 years of age) started out with more knowledge than older patients and that the younger patients retained significant knowledge at follow-up whereas the older patients did not. The authors felt the patients did not learn the information deemed most relevant.

In summary, the investigators who informed schizophrenic patients felt that the patients did not adequately learn the information presented to them. We undertook this investigation to see whether a standardized informing process would improve the level of information schizophrenic outpatients had about neuroleptic medication, particularly the risk of tardive dyskinesia, and to determine whether the patients would maintain this knowledge over time.

Received May 11, 1988; revision received Dec. 21, 1988; accepted Jan. 12, 1989. From the Departments of Psychiatry, Mount Sinai Hospital and Clarke Institute of Psychiatry, Toronto, and Montreal General Hospital. Address reprint requests to Dr. Kleinman, Department of Psychiatry, Mount Sinai Hospital, Rm. 937, 600 University Ave., Toronto, Ont., Canada M5G 1X5.

Copyright © 1989 American Psychiatric Association.

METHOD

The study was conducted at a university-based general hospital. Patients were selected from ward follow-up clinics, a chronic care clinic, and a rehabilitation day center. They were eligible for the study if they had a *DSM-III* diagnosis of schizophrenia, were clinically stable outpatients (i.e., no recent deterioration at the time of enrollment in the study), and had been receiving neuroleptic medication for at least 6 months. Theoretically, all these patients should have been informed by conventional methods.

The patients were randomly assigned to two groups. Of the 21 patients in the intervention group, 13 were men and eight were women; their mean \pm SD age was 31.2 ± 8.1 years, and their mean \pm SD time in school was 11.6 ± 1.7 years. After they were read a standardized information form that was developed by us (available on request), they were given a questionnaire. The 27 patients (22 men and five women) in the comparison group only answered the questionnaire; their mean \pm SD age was 32.4 ± 12.2 years, and their mean \pm SD time in school was 10.7 ± 2.7 years.

The multiple-choice questionnaire consisted of 12 statements. For 10, the possible responses were "true," "false," and "don't know," and for two the patient was asked to choose one of four fill-in-the-blank responses or a "don't know" response. Three of the questions addressed the benefits and common side effects of the neuroleptic medication. Nine statements dealt with tardive dyskinesia. All patients were instructed to circle a response for each statement and not to guess (i.e., to circle "don't know" when they were unsure). The questionnaire was scored by only attributing a value for a correct response. All patients were informed that the medication they were taking was a neuroleptic. Nineteen of the 21 patients in the informed group and 23 of the 27 patients in the uninformed group were reevaluated with the questionnaire after a minimum of 6 months.

RESULTS

There were no significant differences between the two groups with respect to age, years in school, sex, and clinical stability during the 6-month period before entering the study. Clinical stability was determined by assessing 1) the need for an increase in medication of 200 mg of chlorpromazine or its equivalent, 2) the necessity of psychiatric admission, or 3) noncompliance with the medication (defined as not taking medication for 2 or more consecutive weeks).

The mean \pm SD questionnaire score of the 21 schizophrenic patients who had been informed (7.6 ± 2.5) was significantly higher than that of the 27 schizophrenic patients who had not been informed (4.2 ± 2.9) ($F=18.0$, $df=1$, 46 , $p=0.0001$). To determine whether these results might be explained by the potentially confounding effects of age, sex, and education and to de-

termine the correlates of knowledge, a general linear regression was performed; even after controlling for these variables, the informing process remained significantly associated with a higher score ($t=-3.83$, $df=44$, $p=0.0004$). Furthermore, more years in school and younger age were also statistically associated with higher scores ($t=-2.33$, $df=44$, $p=0.02$, and $t=-2.35$, $df=44$, $p=0.02$, respectively) but sex was not ($t=-0.68$, $df=43$, $p=0.5$).

The mean follow-up period was 241 days for the uninformed group ($N=23$) and 239 days for the informed group ($N=19$). At this time, the mean \pm SD score of the informed group (6.4 ± 2.6) was again significantly higher than that of the uninformed group (3.9 ± 2.6) ($F=9.9$, $df=1$, 40 , $p=0.003$). These results remained statistically significant even after controlling for the potentially confounding effects of age, sex, education, and days of follow-up. At follow-up, however, only more years in school was significantly associated with more knowledge ($t=2.74$, $df=39$, $p=0.009$). Sex, age, and length of follow-up were not associated with level of knowledge at follow-up.

Before implementing this study, we felt that one statement was particularly relevant because it addressed the potential irreversibility of tardive dyskinesia. The statement was "In a number of patients the abnormal movements of tardive dyskinesia will remain with them for the rest of their lives." Immediately after being read the standardized information form, 81% ($N=17$) of the informed patients gave a correct response to this statement; however, it received a correct response from only 19% ($N=5$) of the uninformed patients. This difference was statistically significant ($\chi^2=18.5$, $df=1$, $p<0.001$). At follow-up, a correct response to this statement was given by 74% ($N=14$) of the informed patients and by 30% ($N=7$) of the uninformed patients ($\chi^2=7.8$, $df=1$, $p=0.005$).

At follow-up, the patients were asked whether they had ever been told about tardive dyskinesia. Significantly more of the informed patients (89%, $N=16$) than the uninformed patients (48%, $N=11$) acknowledged having been informed about tardive dyskinesia ($\chi^2=7.6$, $df=1$, $p=0.006$).

To ascertain whether the intervention had any negative impact, we compared the clinical stability of both groups of patients. We found no between-group differences in the frequency of noncompliance, admission, or requirement for an increase in medication. Furthermore, a series of matched analyses of pre- versus posttreatment comparisons confirmed that neither group had significant changes in the status of psychiatric admissions, medication increase, or noncompliance.

DISCUSSION

Our findings that our formalized informing process increased patients' knowledge about the risks and benefits of neuroleptic medication significantly and that this knowledge was retained at follow-up are in con-

trast to the finding of Munetz and Roth (10) that learning from a formal approach did not persist at follow-up. Our result may reflect a difference either in the two approaches or in our samples. Our patients had a mean age younger than 33 years; Munetz and Roth's patients had a mean age older than 48 years, which suggests that their patients had a more chronic illness. Munetz and Roth's written approach was to have the patient read the consent form or have it read to them by their clinician whereas we always combined written and oral elements. Also, the nature of the information form and the instruments used to measure knowledge were different; they used a series of open-ended questions that were rated, and we used a multiple-choice questionnaire.

Presently, there is no objective standard above which a person is considered to be "informed." The main focus of this study was to assess patients' awareness of the risks of tardive dyskinesia associated with neuroleptic medication. Our results indicate clearly that a notion of tardive dyskinesia had been conveyed to most informed patients. Consistent with what has been shown by others (10, 11), the informing process did not have a negative impact on the clinical stability of the patients.

Only 48% of our uninformed patients stated that they had been informed despite the fact that all patients should have been informed by conventional methods. Perhaps some were informed and forgot. Another possibility is that some patients may not have been informed. In a survey done in 1979, Benson (12) found that only 32% of psychiatrists routinely informed their patients about tardive dyskinesia.

We found a correlation immediately after the informing process and at follow-up between level of education and knowledge about neuroleptic-associated risks of tardive dyskinesia, probably because both educational level and knowledge after an informing process indicate learning ability.

COMMENT

Munetz and Roth (10) point out that for informed consent to be meaningful it is best viewed as an educational process and not as a single isolated event marked by the signing of a consent form. Our study examined the impact of a single informing session.

We are attempting to develop a more standardized process of informing patients, and we believe that a standardized information form can be a valuable tool in this process. First, learning is reinforced by allowing the patient to visually read the form at the same time it is being read aloud. Second, although not an

option in our study, the patient could be allowed to take the information form home and reread it there; any questions could be answered in future appointments. Third, the multiple-choice questionnaire may be used to assess how much information was retained and which information needs to be reinforced. Finally, APA (1) states that good practice requires physicians to note in their records that the risks of prolonged neuroleptic treatment have been carefully considered and reviewed with the appropriate person. A standardized information form allows more precise documentation of what was said but would not necessarily limit the treating psychiatrist, who would be free to add any other information deemed necessary.

Informed consent for neuroleptic medication is unique in medicine inasmuch as long-term neuroleptic use may result in a potentially irreversible side effect in a large percent of patients and because a number of patients requiring this medication have cognitive deficits that may impair their ability to learn about side effects. The challenge is to effectively treat these patients while respecting their individuality and their autonomy. Informing patients about their illnesses and the positive and negative aspects of treatment is the first step in an educational process that may span years.

REFERENCES

1. Task Force on Late Neurological Effects of Antipsychotic Drugs: Tardive dyskinesia: summary of a task force report of the American Psychiatric Association. *Am J Psychiatry* 1980; 137:1163-1172
2. Davis JM: Overview: maintenance therapy in psychiatry, I: schizophrenia. *Am J Psychiatry* 1975; 132:1237-1245
3. Kane JM, Smith JA: Tardive dyskinesia: prevalence and risk factors, 1959 to 1979. *Arch Gen Psychiatry* 1982; 39:473-481
4. Jeste DV, Wyatt RJ: *Understanding and Treating Tardive Dyskinesia*. New York, Guilford Press, 1982
5. Meisel A, Roth LH, Lidz CW: Toward a model of the legal doctrine of informed consent. *Am J Psychiatry* 1977; 134:285-289
6. Geller JL: State hospital patients and their medication—do they know what they take? *Am J Psychiatry* 1982; 139:611-615
7. Soskis DA: Schizophrenic and medical inpatients as informed drug consumer. *Arch Gen Psychiatry* 1978; 35:645-647
8. Grossman L, Summers F: A study of the capacity of schizophrenic patients to give informed consent. *Hosp Community Psychiatry* 1980; 31:205-206
9. Irwin M, Lovitz A, Marder SR, et al: Psychotic patients' understanding of informed consent. *Am J Psychiatry* 1985; 142:1351-1354
10. Munetz MR, Roth LH: Informing patients about tardive dyskinesia. *Arch Gen Psychiatry* 1985; 42:866-871
11. Munetz MR, Roth LH, Cornes CL: Tardive dyskinesia and informed consent: myths and realities. *Bull Am Acad Psychiatry Law* 1982; 10:77-88
12. Benson PR: Informed consent: drug information disclosed to patients prescribed antipsychotic medication. *J Nerv Ment Dis* 1984; 172:642-653

Dopamine Blockade and Clinical Response: Evidence for Two Biological Subgroups of Schizophrenia

Adam Wolkin, M.D., Faouzia Barouche, M.D., Alfred P. Wolf, Ph.D.,
John Rotrosen, M.D., Joanna S. Fowler, Ph.D., Chyng-Yann Shiue, Ph.D.,
Thomas B. Cooper, M.A., and Jonathan D. Brodie, Ph.D., M.D.

Because CNS neuroleptic concentration cannot be directly measured in patients, the relation between clinical response and extent of dopamine receptor blockade is unknown. This relationship is critical in ascertaining whether nonresponse to neuroleptics is the result merely of inadequate CNS drug levels or of more basic biological differences in pathophysiology. Using [¹⁸F]N-methylspiroperidol and positron emission tomography, the authors assessed dopamine receptor occupancy in 10 schizophrenic patients before and after treatment with haloperidol. Responders and nonresponders had virtually identical indices of [¹⁸F]N-methylspiroperidol uptake after treatment, indicating that failure to respond clinically was not a function of neuroleptic uptake or binding in the CNS.

(Am J Psychiatry 1989; 146:905-908)

Although neuroleptics have brought dramatic improvement to the treatment of schizophrenia, there are many schizophrenic patients—perhaps up to one-third—for whom these drugs have limited efficacy (1). Nonresponse to neuroleptics in this subpopulation is a major clinical problem, and the basis for lack of efficacy is poorly understood.

The purpose of this study was to address the question, To what extent do neuroleptics occupy dopamine receptors in nonresponders? Relatively less dopamine blockade (compared to that in responders to neurolep-

tics) would suggest that peripheral pharmacokinetics or blood-brain barrier impermeability underlie nonresponse to treatment. Conversely, comparable levels of dopamine blockade would imply that nonresponse to neuroleptics cannot be attributed to inadequate dopamine receptor blockade. Rather, there may be a subgroup of schizophrenic patients or a stage of the illness in which there are differences in the regulation of dopaminergic activity (such that neuroleptics do not adequately diminish this activity) or in which dopaminergic activity is not necessarily critical to the pathophysiology of schizophrenia.

In order to assess the relation between response to neuroleptics and degree of dopamine receptor blockade, we used positron emission tomography (PET) to estimate striatal uptake of the D₂ radioligand [¹⁸F]N-methylspiroperidol before and after treating a group of schizophrenic patients with haloperidol.

METHOD

The subjects were 10 male schizophrenic inpatients aged 18 to 49 years who met the *DSM-III* criteria and Research Diagnostic Criteria for chronic schizophrenia with either acute or chronic decompensation. Patients were also selected on the basis of past response to neuroleptics so that the sample would ultimately include both responders and nonresponders to neuroleptics. Most subjects had been recently hospitalized; three had been chronically hospitalized. All subjects were in good physical health, as determined by medical history, physical examination, routine laboratory tests, and head CT scan, and gave written informed consent to participate in this study.

The patients did not take any neuroleptics for a minimum of 9 days. Following this neuroleptic washout period, they were rated with the Brief Psychiatric Rating Scale (BPRS) and underwent a pretreatment PET scan. They were then started on haloperidol. The dose was titrated according to clinical response up to a maximum of 100 mg/day so as to obtain a minimum plasma level of at least 10 ng/ml. The minimum plasma level criterion was based on data suggesting this to be within the therapeutic range for haloperidol (2). The

Received Jan. 29, 1988; revisions received Aug. 1 and Dec. 7, 1988; accepted Jan. 5, 1989. From the Psychiatry Service, New York VA Medical Center; the Department of Psychiatry, New York University Medical Center; and the New York State Psychiatric Institute, New York, N.Y.; the Department of Chemistry, Brookhaven National Laboratory, Upton, N.Y.; and the Nathan Kline Institute, Orangeburg, N.Y. Address reprint requests to Dr. Wolkin, 116A, New York VA Medical Center, New York, NY 10010.

Supported in part by the U.S. Department of Energy, NIH grant NS-15638, NIMH grant MH-CRC-30906, and the Veterans Administration.

The authors thank D. Christman, S. Dewey, R. Gard, K. Karlstrom, C. Shea, D. Schlyer, the cyclotron technicians and the nursing staff of the Clinical Research Center at Brookhaven National Laboratory, and Dr. Bernard Salzman and the staff of ward 18N, Bellevue Hospital, for their assistance with these studies.

patients were carefully observed for side effects, which were controlled by either dose reduction or treatment with anticholinergics. Four to 6 weeks after initiation of haloperidol, and after at least 1 week on a fixed dose, each subject underwent a repeat PET scan and a concurrent BPRS rating. The subject's plasma haloperidol level was also determined during the second PET scan.

The PET scan procedure was as follows. The subject's head was positioned parallel to the canthomeatal plane using localizing lasers for alignment and a fitted foam head holder to maintain position (3). Previous studies have demonstrated this to be an accurate method of repositioning (4). Attenuation characteristics were determined by transmission scanning with a ring source of germanium-68/gallium-68. [^{18}F]N-methylspiroperidol was prepared from the cyclopropyl p-nitrophenyl ketone precursor (5), and 4.60 ± 0.87 mCi (specific activity = $0.38\text{--}3.68$ Ci/ μmol) were injected over 10 seconds through an indwelling antecubital cannula. PETT VI data were recorded in the high-resolution mode (center-to-center slice separation = 14.4 mm, transverse resolution = 8×8 mm) over the next 3 hours (6). Four to seven scan epochs of up to 20 minutes' duration were obtained in each of two alternating positions (7-mm offset).

Striatal regions of interest were visually identified on the reconstructed images of the pretreatment scans. The striatal region was defined as a 5×5 pixel box (1.9 cm^2) at the approximate geometric center of both left and right striata on the PET slice in which striatal uptake was most prominent. The cerebellar region was defined as a 10×20 pixel box (15.4 cm^2) centered over the cerebellum. CT scans were used as an additional reference for anatomic localization in determining optimal slice selection for regional analyses. The same coordinates for each region of interest were used for all images from both the first and second PET scans.

Left and right striatal receptor availability for N-methylspiroperidol was estimated by the "ratio index" (slope $\times 100$) of striatal to cerebellar N-methylspiroperidol uptake versus time. Wong et al. (7, 8) have shown that the change in striatal/cerebellar uptake is linear with respect to time and an index of N-methylspiroperidol binding in the striatum. Smith et al. (9) have further shown with [^{18}F]N-methylspiroperidol that this slope is linear for at least 4 hours and is highly correlated to plasma neuroleptic levels. Striatal/cerebellar uptake was determined as the average decay-corrected regional specific activity concentration (nCi/cc) for each scan epoch. The ratio index was determined as the slope of the regression line of striatal/cerebellar uptake on time ($\times 100$).

CT scans were also obtained parallel to the canthomeatal plane. Identical methods for head positioning and stabilization were used, thus ensuring alignment between CT and PET scans. In addition to screening for structural defects, scans were also used to corroborate PET regions of interest and to measure lateral ventricle size. The latter measurement was obtained to

TABLE 1. Demographic and Clinical Data for Five Responders and Five Nonresponders to Haloperidol Treatment

Item	Responders		Non-responders		Analysis	
	Mean	SD	Mean	SD	t ^a	p
Age (years)	25	7	42	5	4.44	0.002
Years since first hospitalization	4	2	19	5	6.58	<0.001
Total BPRS score						
Pretreatment	35	4	42	5	2.18	0.06
Posttreatment	21	4	39	5	6.89	<0.001
Positive symptom score ^b						
Pretreatment	22	2	27	4	2.65	0.03
Posttreatment	11	3	24	5	5.22	0.001
Mean daily haloperidol dose (mg/day)	39	17	55	24	1.20	n.s.
Days treated with haloperidol	37	6	33	5	1.11	n.s.
Final haloperidol level (ng/ml)	32	9	50	33	—	0.42 ^c

^aTwo-tailed test; df=8.

^bSum of scores on BPRS items conceptual disorganization, tension, mannerisms and posturing, grandiosity, hostility, suspiciousness, hallucinatory behavior, uncooperativeness, unusual thought content, and excitement.

^cMann-Whitney U test; U=8.0.

evaluate potential partial volume effects that might bias PET measures of N-methylspiroperidol uptake in striata. Ventricular size was measured on a digitizer both planimetrically for ventricle-brain ratio and by linear measurements of bicaudate/brain width and bifrontal horn/brain width ratios.

Plasma haloperidol levels were determined by a slight modification of the gas-liquid chromatography method of Bianchetti and Morselli (10). Subjects were classified as either responders or nonresponders to haloperidol; the criterion for classifying a subject as a nonresponder was a less than 20% decrease in total BPRS score. Posttreatment striatal uptake (i.e., ratio index values from the second scan) and percent change in striatal uptake from first to second scan were then compared between these two clinical subgroups.

RESULTS

According to the criterion we have mentioned, five subjects (three white and two black) were classified as nonresponders. These subjects had minimal clinical change, while the five other subjects (two white and three black) showed robust antipsychotic effects (mean \pm SD percent decrease in BPRS score = $4\% \pm 9\%$ and $40\% \pm 9\%$, respectively; $t=6.35$, $df=8$, $p<0.001$, two-tailed). Demographic and clinical data for these two groups are shown in table 1. Nonresponders were significantly older. Although nonresponders had more chronic illnesses, they did *not* have predominantly negative-type schizophrenia and, in fact, had more severe pretreatment positive symptoms than did responders (table 1). Consistent with the flexible dose schedule,

TABLE 2. Left and Right Striatal Dopamine Receptor Availability for *N*-Methylspiroperidol Before and After Haloperidol Treatment in Five Responders and Five Nonresponders^a

Ratio Index ^b	Responders		Nonresponders	
	Mean	SD	Mean	SD
Pretreatment				
Left	5.40	0.77	3.80	0.46
Right	5.35	0.79	4.06	0.44
Posttreatment				
Left	0.60	0.20	0.59	0.23
Right	0.60	0.29	0.52	0.29
Percent change				
Left	88.9	3.2	84.4	6.0
Right	88.7	5.3	87.2	6.9

^aMean±SD *r* values for linear fit of slope for pre- and posttreatment PET scans=0.99±0.006 and 0.87±0.11, respectively.

^bSlope×100 of ratio of striatal to cerebellar *N*-methylspiroperidol uptake versus time.

nonresponders had higher mean daily doses of haloperidol. On average, haloperidol plasma levels at the end of treatment were also higher in nonresponders, but there was considerable overlap of individual levels between the two groups and marked variance among nonresponders (ranges for responders and nonresponders=22–42 ng/ml and 10–90 ng/ml, respectively). There were no differences in planimetric or linear measures of ventricular size between responders and nonresponders.

Ratio index values for striatal *N*-methylspiroperidol uptake are shown in table 2. Pretreatment ratio indices were lower in nonresponders. After haloperidol treatment, specific binding decreased approximately 85%. Posttreatment ratio index values were virtually identical for responders and nonresponders, as was percent blockade (percent change from baseline).

DISCUSSION

In clinical practice, nonresponse is commonly assumed to reflect an inadequate drug level, with consequent use of increasingly larger neuroleptic doses (11, 12). This assumption is supported by marked intersubject variation in neuroleptic metabolism and plasma levels as well as uncertainty (due to the lack of any direct method of measurement) about how much neuroleptic actually enters the brain in nonresponders (13). Clearly, these factors may be crucial in potential responders for whom a minimum drug concentration is needed for antipsychotic efficacy. However, the corollary argument—that nonresponse is due to inadequate drug levels—appears to be not necessarily correct.

The identical mean ratio index values for responders and nonresponders that we found indicate quite comparable levels of dopamine blockade by haloperidol in these sample groups. On average, both groups had almost total blockade, as suggested by posttreatment slope values (ratio index/100) of less than 0.006 (the complete absence of any specific binding to striatum would theoretically result in a zero slope for striatal/

cerebellar uptake versus time). The percent changes in ratio indices were also quite comparable between the two schizophrenic groups and were consistent with other PET data on percent change in neuroleptic ligand binding associated with therapeutic response (14–17).

A flexible haloperidol dose schedule was used so as to maximize the extent of receptor blockade and yet minimize side effects. This resulted in a broad range of haloperidol doses and plasma levels among the nonresponders. Across the entire range of plasma levels among the nonresponders, the corresponding posttreatment ratio index values of receptor availability were equal to or less than all the values for responders. Thus, the lack of response among the nonresponders who had lower doses cannot be attributed to inadequate haloperidol treatment, nor, on the basis of close observation for side effects, is it likely that nonresponse in the subjects with higher doses was due to psychotoxicity.

The pretreatment scans revealed lower ratio index values (i.e., less dopamine receptor availability) in the nonresponders. Wong et al. (7) have previously reported a decrease with age in the slope of striatal/cerebellar uptake versus time that would, in fact, closely predict the average pretreatment values observed here for responders and nonresponders. It may also be that the difference in total receptor availability is a manifestation of biological heterogeneity in these two clinically distinguishable groups.

Several comments about the method should be noted. The washout period was shorter than that which is typically used. However, our data (9) and those of others (18) suggest that this is an adequate washout for *N*-methylspiroperidol measures of receptor binding. Of course, such a washout period does not preclude the possibility of residual changes in receptor density from prior neuroleptic treatment. Such effects might have had a bearing on pretreatment *N*-methylspiroperidol binding (although the greater treatment history in nonresponders would have an effect opposite to the direction of the baseline differences between responders and nonresponders). However, it is most unlikely that these effects had any bearing on the critical measure: comparison of *N*-methylspiroperidol binding after the haloperidol trial.

Second, the number of subjects was small, and the results must naturally be interpreted as preliminary. However, the purpose of this study was simply to determine if dopamine blockade in nonresponders was comparable to that in responders. Our findings clearly establish this point. Further, the virtually identical posttreatment means for both groups imply that there may be a marked overlap, in general, between responders and nonresponders in the extent of blockade. Such an overlap could exist whether the means for all responders and nonresponders are or are not statistically different. We intended no conclusions or inferences about whether such an overall difference might exist.

Several groups (8, 15, 16) have attempted to develop

models for the estimate of dopamine receptor density (B_{max}). This derivative measure is critical in studies such as those reported by Wong et al. (19) and Farde et al. (20), which compared dopamine receptor density in schizophrenic and control subjects. However, it should be noted that each of the approaches to the quantification of ligand binding by using PET, including our own, has pragmatic and conceptual limitations (21, 22). In the present study, we chose a conservative approach that is a quantitative measure of binding although it is not necessarily a direct expression of B_{max} . It was well suited for our study where we were comparing receptor blockade (i.e., *N*-methylspiroperidol binding). We should also emphasize that in our [18 F]*N*-methylspiroperidol studies the ratio index is stable over at least 4 hours and does not suffer from the limitations imposed by the use of 11 C-labeled ligands, in terms of either counting statistics or the blood flow component (23).

Estimates of haloperidol blockade are based on striatal measures, whereas it is assumed that antipsychotic effects of neuroleptics are mediated in mesolimbic and mesocortical dopamine systems, in which measurement of *N*-methylspiroperidol uptake is below the sensitivity of present PET methodology. However, many of the data on the mechanism of action of neuroleptics—including the strong correlation between dopamine receptor affinity and clinical potency (24)—have been based on striatal preparations. This implies that neuroleptic efficacy is associated with blockade of the same class of D_2 receptors as are visualized in the striatum with *N*-methylspiroperidol. While the dynamics of D_2 receptor blockade may vary from system to system because of differences in pre- and postsynaptic regulatory mechanisms, comparable degrees of neuroleptic blockade are expected to occur within the same receptor subclass.

In summary, the data in this paper are the most direct evidence to date to suggest that nonresponse to neuroleptics may not necessarily be due to inadequate neuroleptic blockade. Rather, the similarity in receptor blockade between responders and nonresponders could reflect an intrinsic difference in the pathophysiology of schizophrenic symptoms. This is in keeping either with the consensus that the disease is heterogeneous or with the possibility that it is an evolving illness with different pathophysiological stages (25, 26).

REFERENCES

- Jus A, Villeneuve A, Jus K: Therapeutic dilemma in neuroleptic-resistant psychotic disorders, in *Neuropsychopharmacology*, vol 1. Edited by Deniker P, Radouco-Thomas C, Villeneuve A. Oxford, Pergamon Press, 1978
- Guthrie S, Lane EA, Linnoila M: Monitoring of plasma drug concentrations in clinical psychopharmacology, in *Psychopharmacology: The Third Generation of Progress*. Edited by Meltzer HY. New York, Raven Press, 1987
- Kearfott KJ, Rottenberg DA, Knowles RJR: A new headholder for PET, CT, and NMR imaging. *J Comput Assist Tomogr* 1984; 8:1217–1220
- Bartlett EJ, Brodie JD, Wolf AP, et al: Reproducibility of cerebral glucose metabolic measurements in resting human subjects. *J Cereb Blood Flow Metabol* 1988; 8:502–512
- Shiue C-Y, Fowler JS, Wolf AP, et al: No-carrier-added fluorine-18-labeled *N*-methylspiroperidol: synthesis and biodistribution in mice. *J Nucl Med* 1986; 27:226–234
- Ter-Pogossian MM, Ficke DC, Hood JT, et al: PETT VI: a positron emission tomograph utilizing cesium fluoride scintillation detectors. *J Comput Assist Tomogr* 1982; 6:125–133
- Wong DF, Wagner HN, Dannals RF, et al: Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. *Science* 1984; 226:1393–1396
- Wong DF, Gjedde A, Wagner HN: Quantification of neuroreceptors in the living human brain, I: irreversible binding of ligands. *J Cereb Blood Flow Metab* 1986; 6:137–146
- Smith M, Wolf AP, Brodie JD, et al: Serial [18 F]-*N*-methylspiroperidol PET studies to measure changes in antipsychotic drug D_2 receptor occupancy in schizophrenic patients. *Biol Psychiatry* 1988; 23:653–663
- Bianchetti G, Morselli PL: Rapid and sensitive method for determination of haloperidol in human samples using nitrogen-phosphorus selective detection. *J Chromatogr* 1978; 153:203–209
- Baldessarini RJ, Cohen BM, Teicher MH: Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Arch Gen Psychiatry* 1988; 45:79–91
- Davis JM, Ericksen SE, Hurt S, et al: Haloperidol plasma levels and clinical response: basic concepts and clinical data. *Psychopharmacol Bull* 1985; 21:48–51
- Davis JM, Ericksen S, Dekirmenjian H: Plasma levels of antipsychotic drugs and clinical response, in *Psychopharmacology: A Generation of Progress*. Edited by Lipton MA, DiMascio A, Killam KF. New York, Raven Press, 1978
- Wong DF, Wagner HN, Coyle J, et al: Assessment of dopamine receptor blockade by neuroleptic drugs in the living human brain (abstract). *J Nucl Med* 1985; 26:52
- Farde L, Hall H, Ehrin E, et al: Quantitative analysis of D_2 dopamine receptor binding in the living human brain by PET. *Science* 1986; 231:258–261
- Wong DF, Gjedde A, Wagner HN, et al: Quantification of neuroreceptors in the living human brain, II: inhibition studies of receptor density and affinity. *J Cereb Blood Flow Metab* 1986; 6:147–153
- Farde L, Wiesel W, Halldin C, et al: Central D_2 -dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. *Arch Gen Psychiatry* 1988; 45:71–76
- Cambron H, Baron JC, Boulenger JP, et al: In vivo assay for neuroleptic receptor binding in the striatum. *Br J Psychiatry* 1987; 151:824–830
- Wong DF, Wagner HN, Tune LE, et al: Positron emission tomography reveals elevated D_2 dopamine receptors in drug-naïve schizophrenics. *Science* 1986; 234:1558–1563
- Farde L, Wiesel F-A, Hall H, et al: No D_2 receptor increase in PET study of schizophrenia (letter). *Arch Gen Psychiatry* 1987; 44:671–672
- Swart JAA, Korf J: In vivo dopamine receptor assessment for clinical studies using positron emission tomography. *Biochem Pharmacol* 1987; 36:2241–2250
- Perlmutter JS, Larson KB, Raichle ME, et al: Strategies for in vivo measurement of receptor binding using positron emission tomography. *J Cereb Blood Flow Metab* 1986; 6:154–169
- Arnett CD, Wolf AP, Shiue C-Y, et al: Improved delineation of human dopamine receptors using [18 F]-*N*-methylspiroperidol and PET. *J Nucl Med* 1986; 27:1878–1882
- Seeman P, Lee T: Antipsychotic drugs: direct correlations between clinical potency and presynaptic action on dopamine neurons. *Science* 1975; 188:1217–1219
- Meltzer HY: Biology of schizophrenia: a review and proposal for method of study. *Schizophr Bull* 1979; 5:460–478
- Buchsbaum MS, Rieder RO: Biologic heterogeneity and psychiatry research. *Arch Gen Psychiatry* 1979; 36:1163–1169

Open Trial of Fluoxetine in Obsessive-Compulsive Disorder

Michael A. Jenike, M.D., Lynn Buttolph, M.D., Ph.D., Lee Baer, Ph.D.,
Joseph Ricciardi, and Amy Holland

A 12-week open trial of fluoxetine in 61 obsessive-compulsive disorder patients significantly improved depressive and obsessive-compulsive symptoms. Baseline depression scores were not related to improvement on two obsessive-compulsive scales. The results reinforce the hypothesis of serotonergic abnormalities in obsessive-compulsive disorder.

(Am J Psychiatry 1989; 146:909-911)

Clomipramine (1-4) and fluvoxamine (5, 6), both serotonergic agonists, are effective in treating patients with obsessive-compulsive disorder. Since fluoxetine also inhibits presynaptic uptake of serotonin and has a low side effect profile, its effectiveness in obsessive-compulsive patients merits study.

Two small trials suggest at least some efficacy for fluoxetine. Turner et al. (7) gave fluoxetine to 10 obsessive-compulsive patients and found that it affected depressive symptoms and also had a nonsignificant effect on self-report measures of obsessions and ritualistic behavior. Fontaine and Chouinard (8) performed a 9-week open trial of fluoxetine in nine obsessive-compulsive patients and reported a significant improvement in obsessional symptoms. We have over 150 well-characterized patients with obsessive-compulsive disorder who are taking fluoxetine in an open trial, and since initial findings appear favorable, we report the results of the first 61 patients who completed the 12-week trial.

METHOD

Sixty-one outpatients fulfilling DSM-III-R criteria and Research Diagnostic Criteria for obsessive-compulsive disorder (34 men and 27 women; mean \pm SD age, 36.5 \pm 10.7 years) completed the 12-week trial. All subjects had had obsessive-compulsive disorder for more than 1 year. The patients were advised that although fluoxetine is not an experimental drug, it had not been used extensively in patients with obsessive-compulsive disorder.

Fluoxetine was administered as tolerated: week 1, 20 mg in the morning; weeks 2-4, 20 mg in the morning and 20 mg in the afternoon; week 5, 40 mg in the morning and 20 mg in the afternoon; and weeks 6-12, 40 mg in the morning and 40 mg in the afternoon.

At baseline and every 4 weeks thereafter, the following scales were administered: the Yale-Brown Obsessive-Compulsive Scale (the main dependent variable in multicenter trials of clomipramine, sertraline, and fluvoxamine, available from Wayne Goodman, M.D., Yale University), the Maudsley Obsessional-Compulsive Inventory (4), and the Beck Depression Inventory (9), a self-administered instrument. At 4-week intervals, patients were carefully questioned about side effects.

Changes in obsessive-compulsive and depressive symptoms were assessed by a series of analyses of variance (ANOVA). The Beck scale was analyzed by a one-factor ANOVA with repeated measures. Because we were interested in the effect of baseline levels of depression on improvement of obsessive-compulsive symptoms, the two obsessive-compulsive scales, Yale-Brown and Maudsley, were analyzed by a two-factor ANOVA with repeated measures on one factor (occasions) and presence of depression used as a group factor. All subjects were categorized into either a nondepressed group or a depressed group on the basis of baseline Beck scale scores of less than 11 for the nondepressed group and greater than or equal to 11 for the depressed group.

Received Aug. 29, 1988; revision received Jan. 10, 1989; accepted Jan. 13, 1989. From the Harvard Medical School, Obsessive-Compulsive Disorders Clinic and Research Unit, Massachusetts General Hospital. Address reprint requests to Dr. Jenike, OCD Clinic and Research Unit, Bulfinch 3, Massachusetts General Hospital, Fruit Street, Boston, MA 02114.

Copyright © 1989 American Psychiatric Association.

TABLE 1. Change in Obsessive-Compulsive and Depressive Symptoms of 61 Patients With Obsessive-Compulsive Disorder During a 12-Week Open Trial of Fluoxetine

Scale	Score							
	Baseline		Week 4		Week 8		Week 12	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Beck Depression Inventory	16.9	9.6	12.7 ^a	8.1	11.2 ^a	8.7	9.1 ^a	9.2
Yale-Brown Obsessive-Compulsive Scale	22.2	6.2	20.2 ^a	6.9	15.9 ^a	6.9	13.9 ^a	7.0
Maudsley Obsessive-Compulsive Inventory	15.4	5.3	15.1	5.1	13.1 ^a	5.3	12.7 ^a	5.3

^aSignificantly different from baseline score by Sheffé post hoc F test ($p < 0.05$).

RESULTS

Of 72 patients entering the study, 61 patients completed the 12-week trial and 11 dropped out before the 1-month assessment. The reasons for dropping out included transfer of care out of state, $N=1$; increased anxiety, $N=1$; fatigue, $N=1$; insomnia, $N=2$; weight loss, $N=1$; and medication noncompliance, $N=5$. The side effects experienced by some of the remaining 61 patients included fatigue, $N=6$; anxiety, $N=2$; sexual dysfunction, $N=5$; nausea, $N=3$; insomnia, $N=5$; loss of appetite, $N=1$; weight loss, $N=2$; tremor, $N=5$; transient mild rash, $N=1$; racing heart, $N=2$; and chest tightness, $N=1$. Some had more than one side effect, and 31 patients (51%) did not complain of side effects. Side effects were managed with reassurance and/or dose adjustments. The mean \pm SD maximal dose of fluoxetine was 75.1 ± 11.3 mg/day for the 61 patients. Fifty patients reached a dose of 80 mg/day.

An ANOVA of Beck scale scores yielded a significant occasions effect ($F=38.0$, $df=3$, 180, $p < 0.0001$), indicating a significant decline in depression scores over the 12-week study. Post hoc Sheffé F tests indicated significant declines in depression scores from baseline to week 4, week 8, and week 12 (table 1).

An ANOVA found a nonsignificant group effect on the Yale-Brown scale ($F=1.3$, $df=1$, 59), indicating no overall mean difference between the nondepressed ($N=19$) and depressed ($N=42$) groups. The occasions effect on this scale was significant ($F=62.8$, $df=3$, 177, $p < 0.0001$), indicating a significant decline in scores over the 12-week study, regardless of group. The interaction effect (Group \times Occasions) was not significant ($F=1.8$, $df=3$, 177), indicating no difference in the pattern of change over time for the nondepressed and depressed groups (table 1). Sheffé post hoc F tests yielded significant declines in Yale-Brown scale scores between baseline and weeks 4, 8, and 12 (table 1).

An ANOVA found a nonsignificant group effect on the Maudsley scale ($F=2.9$, $df=1$, 59), indicating no overall differences between the two groups. The interaction (Group \times Occasions) effect was also nonsignificant ($F=0.2$, $df=3$, 177), indicating no difference in the pattern of change over time for the two groups. The occasions effect was significant ($F=17.2$, $df=3$, 177, $p < 0.0001$), indicating a decrease in scores over the 12-week study, regardless of group. Sheffé post hoc F tests yielded a significant decline between baseline

and weeks 8 and 12 (but not week 4) for the entire sample (table 1).

Change scores were calculated between baseline and week 12 for all three dependent variables. Change in Yale-Brown scale scores was correlated with change in Maudsley scale scores ($r=0.60$, $N=61$, $p < 0.01$) and in Beck scale scores ($r=0.45$, $N=61$, $p < 0.01$). Change in Maudsley scale scores was correlated with change in Beck scale scores ($r=0.40$, $N=61$, $p < 0.01$). Thus, reduction in depression was strongly related to changes in both obsessive-compulsive measures, which were themselves highly correlated.

DISCUSSION

Fluoxetine produced a significant overall reduction in symptoms of both obsessive-compulsive disorder and depression. On the Yale-Brown scale and the Maudsley scale, depressed and nondepressed patients showed equal improvement in obsessive-compulsive scores. Fluoxetine's antidepressant effects are well documented (10), and these preliminary data suggest that fluoxetine acts similarly on obsessive-compulsive symptoms for depressed and nondepressed patients.

Because fluoxetine is a serotonergic agonist that inhibits presynaptic uptake of serotonin (10), our apparent success with fluoxetine lends support to the hypothesis that serotonergic abnormalities exist in at least some patients with obsessive-compulsive disorder. Further investigation with specific serotonergic agonists and antagonists is warranted (2, 3), and efficacy studies involving medications with effects on a variety of neurotransmitter systems are also required to ascertain whether an ability to enhance serotonin activity is a necessary property for antiobsessional activity (3).

Fluoxetine may be an effective treatment for obsessive-compulsive disorder. Until more definitive data on efficacy and optimal dose are available, clinicians may wish to try a trial of fluoxetine for their patients with obsessive-compulsive disorder.

REFERENCES

1. Jenike MA: Somatic treatments, in *Obsessive Compulsive Disorders: Theory and Management*. Edited by Jenike MA, Baer L, Minichiello WE. Littleton, Mass, PSG, 1986
2. Zohar J, Insel TR, Zohar-Kadouch RC, et al: Serotonergic re-

- sponsivity in obsessive-compulsive disorder: effects of chronic clomipramine treatment. *Arch Gen Psychiatry* 1988; 45:167-172
3. Charney DS, Goodman WK, Price LH, et al: Serotonin function in obsessive-compulsive disorder: a comparison of the effects of tryptophan and m-chlorophenylpiperazine in patients and healthy subjects. *Arch Gen Psychiatry* 1988; 45:177-185
 4. Thoren P, Asberg M, Cronholm B, et al: Clomipramine treatment of obsessive-compulsive disorder, I: a controlled clinical trial. *Arch Gen Psychiatry* 1980; 37:1281-1285
 5. Perse TL, Griest JH, Jefferson JW, et al: Fluvoxamine treatment of obsessive-compulsive disorder. *Am J Psychiatry* 1987; 144:1543-1548
 6. Price LH, Goodman WK, Charney DS, et al: Treatment of severe obsessive-compulsive disorder with fluvoxamine. *Am J Psychiatry* 1987; 144:1059-1061
 7. Turner SM, Jacob RG, Beidel DC, et al: Fluoxetine treatment of obsessive-compulsive disorder. *J Clin Psychopharmacol* 1985; 5:207-212
 8. Fontaine R, Chouinard G: An open clinical trial of fluoxetine in the treatment of obsessive-compulsive disorder. *J Clin Psychopharmacol* 1986; 6:98-100
 9. Beck AT, Ward CH, Mendelson M, et al: An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 41:561-571
 10. Bremner JD: Fluoxetine in depressed patients: a comparison with imipramine. *J Clin Psychiatry* 1984; 45:414-419

Elevated Antidepressant Plasma Levels After Addition of Fluoxetine

Robert B. Aranow, M.D., James I. Hudson, M.D., Harrison G. Pope, Jr., M.D.,
Tana A. Grady, M.D., Thomas A. Laage, M.D.,
Iris R. Bell, M.D., Ph.D., and Jonathan O. Cole, M.D.

Four patients treated with tricyclic antidepressants and one patient treated with trazodone all demonstrated marked increases in plasma levels of these drugs after the addition of fluoxetine. Such increases could increase adverse effects.

(*Am J Psychiatry* 1989; 146:911-913)

Fluoxetine is an antidepressant recently approved for commercial use in the United States. Although fluoxetine generally produces few side effects when administered alone (1), there have been few studies of its effects when used in combination with other psychotropic agents.

Recently an elderly patient at our hospital was reported to have developed a markedly elevated desipramine plasma level after the addition of fluoxetine (2).

This observation raised the question of whether fluoxetine affects the metabolism of other antidepressants and prompted us to seek additional cases in which fluoxetine was given in combination with tricyclics or trazodone. We found five such cases in which antidepressant plasma levels were measured before and after fluoxetine was added to an existing regimen of tricyclics or trazodone.

CASE MATERIAL

All of the patients received diagnoses of major depression; patient 2 had psychotic features, and patient 3 received an additional diagnosis of borderline personality disorder. Other demographic and clinical characteristics of the five patients are presented in table 1. All initially received trials of tricyclics (patients 1-4) or trazodone (patient 5). Patient 1 was not able to tolerate nortriptyline because of sedation; fluoxetine was added while nortriptyline was being tapered, with the intention of discontinuing nortriptyline. In the case of patient 2, imipramine was effective but was discontinued because of anticholinergic side effects; fluoxetine was subsequently started, and later imipramine was reintroduced because fluoxetine proved to be ineffective alone. In the other three cases, fluoxetine was

Received July 20, 1988; revision received Dec. 7, 1988; accepted Jan. 5, 1989. From the Laboratories for Psychiatric Research and the Affective Disease Program, McLean Hospital, and the Department of Psychiatry, Harvard Medical School, Boston. Address reprint requests to Dr. Aranow, McLean Hospital, Belmont, MA 02178.

Supported in part by NIMH Mental Health Clinical Research Center grant MH-36224.

Copyright © 1989 American Psychiatric Association.

TABLE 1. Clinical Characteristics and Antidepressant Blood Levels of Five Patients Before and After Addition of Fluoxetine^a

Patient	Age (years)	Sex	Fluoxetine Dose (mg/day)	Drug	Drug Plasma Level and Dose						
					Before Fluoxetine			After Fluoxetine			Increase in Ratio (%)
					Level (ng/ml)	Dose (mg/day)	Ratio	Level (ng/ml)	Dose (mg/day)	Ratio	
1	39	F	20	Nortriptyline	108	100	1.1	289 167 ^b	125 50	2.3 3.3	109 200
2	42	F	60	Imipramine	100 ^c	150	0.7	206 ^d	50	4.1	486
3	42	F	40	Nortriptyline	79	100	0.8	330	150	2.2	175
				Carbamazepine	6.9	300	0.023	9.9	400	0.025	9
4	30	M	20 10 ^c	Desipramine	250	300	0.8	390 506 ^c	300 300	1.3 1.7	63 113
5	82	F	40	Trazodone	2150	175	12.3	2016	125	16.1	31

^aAdverse reactions were experienced by patient 2 (anticholinergic effects), patient 4 (constipation and urinary hesitancy), and patient 5 (sedation and unstable gait).

^bSecond plasma level determined 7 days after the previous measurement.

^c37 ng/ml of imipramine and 63 ng/ml of desipramine.

^d117 ng/ml of imipramine and 89 ng/ml of desipramine.

^eFluoxetine dose reduced to 20 mg every other day during this period; second level determined 5 days after the previous measurement.

added to the previous antidepressant to improve on a partial response (patients 3 and 4) or poor response (patient 5) to that agent.

Antidepressant plasma levels were determined with high-performance liquid chromatography by the Psychiatric Chemistry Laboratory at the New England Deaconess Hospital, Boston. In this laboratory, the coefficient of variation (standard deviation/mean \times 100) for plasma levels of the specific antidepressants taken by our five patients ranged from 3.5% to 6.4%. The samples drawn before and after treatment with fluoxetine were obtained 12 hours after the last dose of medication, after all drug doses had been stable for at least 1 week. In patients 1 and 2 the levels increased despite a decrease in antidepressant dose, in patients 3 and 4 the level increased markedly when the dose was unchanged or had only been increased modestly, and in patient 5 the level remained about the same despite a decrease in dose. After the addition of fluoxetine, the ratio of antidepressant plasma level to dose increased by 109%–486% in the four patients taking tricyclics and by 31% in the patient taking trazodone. These changes were evident clinically in three patients, who reported adverse effects characteristic of their initial antidepressant within 7 to 14 days of the addition of fluoxetine. Patient 2 developed anticholinergic effects, patient 4 experienced constipation and urinary hesitancy, and patient 5 experienced sedation and unstable gait.

Also of note is that patient 3 was receiving carbamazepine in addition to nortriptyline and fluoxetine. However, the ratio of carbamazepine plasma level to dose remained relatively stable after fluoxetine was added.

DISCUSSION

In four patients receiving tricyclics and one receiving trazodone, the addition of fluoxetine was associated with markedly increased plasma levels of the other antidepressants. Similar findings have been reported in one additional patient at our center (2) and in two patients at another center (3). These observations are important because fluoxetine will likely be combined with these antidepressants in clinical practice, either in the hopes of augmenting a partial response (as in our patients 3 and 4) or in the course of tapering the previous agent (as with patient 1). Such abrupt increases in plasma levels of tricyclics and trazodone may have significant clinical consequences, either in the form of increased anticholinergic or sedative effects (as in three of our cases) or, conceivably, in the form of more serious effects, such as the cardiotoxicity and lowered seizure threshold associated with high tricyclic plasma levels (4).

The mechanism for the apparent increase in antidepressant level after addition of fluoxetine is unknown. However, a likely hypothesis is that fluoxetine is acting to decrease hepatic metabolism of other antidepressants—a common interaction of hepatically metabolized compounds (5). Although direct hepatotoxicity cannot be excluded, none of the patients had signs of liver failure, and hepatic enzyme levels were normal in the one patient (patient 3) in whom they were measured. Also of interest is that in the one patient receiving carbamazepine, which is also metabolized by the liver, the ratio of plasma level to dose was relatively unaffected by the addition of fluoxetine, suggesting that fluoxetine may have different effects on the metabolism of various agents.

Several limitations of our case material should be discussed. First, we obtained data only on patients whose antidepressant levels had been measured both before and after fluoxetine treatment. Physicians might be more likely to obtain blood level measurements after fluoxetine treatment if adverse reactions were suspected (as in patients 2, 4, and 5 in our series) and thus select for patients with elevated levels. On the other hand, in two of our cases blood levels were determined for reasons other than adverse reactions. Second, because the doses of medication were not identical throughout the period of observation, we cannot estimate accurately the quantitative effect of fluoxetine on the levels of other antidepressants. Third, the possibility remains that the observed elevations of tricyclic and trazodone plasma levels were simply a testing artifact caused by the presence of fluoxetine and its metabolites. However, in view of the adverse effects described by three of the five patients, this possibility seems unlikely.

It should be noted that alternative antidepressant therapies, such as lithium and thyroid augmentation, might also have been tried in these cases, but it is beyond the scope of this paper to discuss the various

alternative psychopharmacological strategies that might have been considered.

Our experience should alert practitioners to the possibility that fluoxetine may decrease the metabolism of other antidepressant agents and thereby has the potential to cause adverse reactions. We hope these observations will stimulate interest in further studies of the mechanism and magnitude of this interaction.

REFERENCES

1. Schatzberg AF, Dessain E, O'Neil P, et al: Recent studies on selective serotonergic antidepressants: trazodone, fluoxetine and fluvoxamine. *J Clin Psychopharmacol* 1987; 7:44S-49S
2. Bell IR, Cole JO: Fluoxetine induces elevation of desipramine and exacerbation of geriatric nonpsychotic depression. *J Clin Psychopharmacol* 1988; 8:447-448
3. Vaughan DA: Interaction of fluoxetine with tricyclic antidepressants (letter). *Am J Psychiatry* 1988; 145:1478
4. Klein DF, Gittelman R, Quitkin F, et al: *Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children*, 2nd ed. Baltimore, Williams & Wilkins, 1980
5. Amsterdam J, Brunswick D, Mendels J: The clinical application of tricyclic antidepressant pharmacokinetics and plasma levels. *Am J Psychiatry* 1980; 137:653-662

Adjunctive Buspirone in Benzodiazepine Treatment of Four Patients With Panic Disorder

David R. Gastfriend, M.D., and Jerrold F. Rosenbaum, M.D.

Four patients with panic disorder whose panic attacks responded to benzodiazepine treatment but who suffered persistent anxiety improved after addition of buspirone. Despite its lack of antipanic effect, buspirone may offer an adjunctive benefit when added to benzodiazepines in panic disorder.

(Am J Psychiatry 1989; 146:914-916)

Buspirone, a new nonbenzodiazepine anxiolytic, is reportedly as effective for generalized anxiety as diazepam (1). Like the benzodiazepines, buspirone has antiaggressive and anticonflict effects in animals. Buspirone is thought to lack potential for abuse because it produces less euphoria and sedation than diazepam and may produce dysphoria at higher doses (e.g., 40 mg). Also, users of sedative drugs for recreational purposes and alcoholics show little interest in abusing or overusing this agent (2).

Given its comparable anxiolytic efficacy and lack of potential for abuse, buspirone would seem destined to replace benzodiazepines in the antianxiety armamentarium. However, increasing clinical experience suggests that this is not the case, and patients with previous benzodiazepine exposure, in particular, may do less well with buspirone. For example, in a retrospective review of 50 patients with refractory anxiety as part of their clinical picture, only 10% had a satisfactory clinical result (W. Falk, personal communication). Rickels et al. (3) have suggested that patients with "virgin anxiety"—those with no prior benzodiazepine treatment or no preformed expectations of sedation or immediate anxiolysis—and those patients who are less chronically anxious may respond best to buspirone.

Clinical trials indicate that buspirone is ineffective as a sole treatment for panic disorder (4). We now report on a series of four consecutive patients with DSM-

III-R panic disorder; these patients, in the practice of one clinician (D.R.G.), had incomplete relief of anxiety when given benzodiazepines and substantially improved when buspirone was added to their benzodiazepine regimens.

CASE REPORTS

Case 1. Mr. A, a 43-year-old man who had had panic attacks and agoraphobia since he was in his late thirties, appeared to be responding to 7 mg/day of alprazolam until his pharmacist revealed that the patient had altered alprazolam prescriptions to obtain higher doses. Neither imipramine, 200 mg/day (plasma levels of imipramine plus desipramine=248 µg/liter), nor maprotiline, 300 mg/day (plasma level=289 µg/liter) for 8 weeks, nor clonazepam, 0.5 mg t.i.d. for 2 weeks, was effective, and Mr. A requested "another chance" with alprazolam. Alprazolam, 1 mg q.i.d., partially reduced his panic attacks, but generalized anxiety persisted. When he requested an increased dose of alprazolam, citing job stress, buspirone, 5 mg t.i.d., was added instead. Within 2 weeks he suggested that "it might be helping." Over the next 9 months, despite purchasing a home and taking a second job, he continued to report that buspirone allowed him to "more easily control residual attacks; they're less intense, I feel more at ease"; this improvement was maintained without further increase in the dose of alprazolam.

Case 2. Ms. B, a 47-year-old woman who felt "nervous most of the time, day and night," had suffered separation anxiety in childhood, school phobia, and panic attacks (up to several per week) and was completely unable to walk outside her home, shop, or travel alone. Her internist had prescribed diazepam, 5 mg b.i.d., for 13 years, but her symptoms were exacerbated during her boyfriend's illness. Prohibitive side effects emerged with clonazepam, 1 mg t.i.d.; phenelzine, 45 mg/day; imipramine, 175 mg/day; desipramine, 100 mg/day; and nortriptyline, 100 mg/day. The dose of diazepam was increased to 30 mg/day, but the panic attacks persisted and she remained severely dysfunctional.

Two weeks after the addition of buspirone, 5 mg/day b.i.d., Ms. B reported feeling much less frightened and spontaneously began walking outside her home, crossing streets, and shopping alone for the first time in many years. Despite mild headaches and orthostatic lightheadedness, she uncharacteristically asked to increase the dose of buspirone to 10 mg t.i.d. rather than to increase the diazepam. She remained markedly improved at these doses for the 9-month duration of follow-up.

Received Sept. 8, 1988; revision received Dec. 21, 1988; accepted Jan. 12, 1989. From the Clinical Psychopharmacology Unit and the West End Group Practice, Psychiatry Service, Massachusetts General Hospital, and the Department of Psychiatry, Harvard Medical School, Boston. Address reprint requests to Dr. Gastfriend, West End Group Practice, ACC 712, Massachusetts General Hospital, Boston, MA 02114.

Copyright © 1989 American Psychiatric Association.

TABLE 1. Effects of Adjunctive Buspirone in Four Patients Treated With Benzodiazepines for Panic Disorder

Case	Diagnosis	Benzodiazepine Use Before Buspirone (years)	Clinical Global Severity Score ^a		Benzodiazepine Dose Outcome With Buspirone	Duration of Buspirone Effect (months)	Side Effects of Buspirone
			Before Buspirone	After Buspirone			
1	Panic disorder with agoraphobia, benzodiazepine dependence	3	4	3	75% reduction	12	None
2	Panic disorder with agoraphobia, generalized anxiety	>10	7	5	Stabilized	4	Headache, lightheadedness
3	Panic disorder with agoraphobia, alcohol dependence in remission, social phobia	1.5	4	2	Discontinued	5	Nausea, forgetfulness
4	Panic disorder with agoraphobia, generalized anxiety	4.5	4	2	50% reduction	7	Sedation

^a1=not at all ill; 7=among the most extremely ill.

Case 3. Mr. C, a 27-year-old man, had a history of separation anxiety in childhood, panic attacks beginning at age 15, and alcohol dependence, which remitted when he was in his early twenties. At age 25 he presented with panic attacks, social phobia, partial avoidance of venturing outside his apartment alone, and dysthymia. Desipramine, 175 mg/day, and clonazepam, 0.5 mg b.i.d., suppressed his panic. He began working, but social-phobic symptoms compromised his job performance, and persisting drowsiness precluded increases in the dose of clonazepam. Buspirone, 5 mg t.i.d., was added, and Mr. C experienced subjective improvement in his social phobia and cessation of drowsiness. The clonazepam was gradually withdrawn over the next 4 weeks. Although he attributed mild forgetfulness and rare nausea to the buspirone, he felt he tolerated job stress better and stated, "I would not want to go off this."

Case 4. Ms. D, a 42-year-old woman, had an 11-year history of panic attacks and phobic avoidance. Desipramine, 250 mg/day (plasma level=171 µg/liter), and alprazolam, 4 mg/day, gave complete blockade of panic, but anticipatory and free-floating anxiety persisted despite her progress in shopping and driving during gradual exposure to these activities. Because of her anxiety, she began consuming four or five mixed drinks on most evenings. Then she stopped drinking but gradually increased her dose of alprazolam to 6 mg/day. Buspirone, 5 mg t.i.d., was then added to her regimen. Within 4 weeks she felt calm, had no difficulty falling asleep, and began decreasing her dose of alprazolam. Over the next 4 months, she reduced her dose of alprazolam to 4 mg/day and stated, "I almost think the buspirone is more helpful than the alprazolam."

DISCUSSION

In these four patients with panic disorder, chronic anxiety symptoms, and long-term benzodiazepine treatment, the addition of buspirone improved anticipatory and generalized anxiety. Relief of panic was attributed to other agents. Buspirone permitted benzodiazepine dose reductions in three of the patients, including one who had altered alprazolam prescriptions to increase his dose. None of the patients would agree to a trial discontinuation of buspirone for the purpose of documenting its efficacy. None experienced aug-

mented symptoms or jitteriness from buspirone (5), possibly because of the concomitant treatment with a benzodiazepine. The anxiolytic effect of buspirone has been sustained in these patients for a mean of 7 months of follow-up. Subsequently, in three similar cases of patients treated by members of our group, one showed marked improvement, one equivocal improvement, and one no improvement.

Since buspirone does not protect against benzodiazepine withdrawal symptoms and is not an anticonvulsant, patients must be cautioned to reduce the benzodiazepine gradually and to anticipate possible rebound or withdrawal symptoms such as increased autonomic arousal, insomnia, and tremulousness. Also, for patients maintained on benzodiazepines, buspirone is probably best introduced as a concomitant agent, so that the clinical picture (including buspirone side effects) is not confused by benzodiazepine withdrawal.

Several mechanisms may explain the adjunctive clinical effect of buspirone. Buspirone has high affinity for the serotonin (5-HT) type 1a receptor, where it has predominantly agonist effects. Both benzodiazepines and (to a greater extent) buspirone reduce dorsal raphe nucleus activity (6), which is thought to reduce behavioral inhibition; thus, combined use of benzodiazepines and buspirone may offer additive potency. Buspirone may have antidepressant properties (7, 8), which may have improved the mood and general well-being of these patients. In contrast to the benzodiazepines, buspirone increases locus ceruleus firing (9). Studies report subjective and objective improvement in alertness and concentration and reduced confusion in patients taking buspirone compared with those taking benzodiazepines (8), and buspirone reduces alcohol-induced impairment (10). It is not known, however, whether the combination of buspirone and a benzodiazepine produces changes in cognition. Buspirone may work adjunctively by increasing alertness and additively by reducing behavioral inhibition.

In summary, these cases suggest a role for buspirone in combination with high-potency benzodiazepines for patients with panic disorder and persisting generalized, anticipatory, or social anxiety.

REFERENCES

1. Rickels K, Weisman K, Norstad N, et al: Buspirone and diazepam in anxiety: a controlled study. *J Clin Psychiatry* 1982; 43(12, section 2):81-86
2. Cole JO, Orzack MH, Beake B, et al: Assessment of the abuse liability of buspirone in recreational sedative users. *J Clin Psychiatry* 1982; 43(12, section 2):69-74
3. Rickels K, Case WG, Schweizer EE, et al: Low-dose dependence in chronic benzodiazepine users: a preliminary report on 119 patients. *Psychopharmacol Bull* 1986; 22:407-415
4. Sheehan DV, Raj AB, Harnett-Sheehan K, et al: The relative efficacy of buspirone, imipramine, and placebo in panic disorder: a preliminary report. *Psychopharmacology, Biochemistry and Behavior* 1988; 29:815-817
5. Liegghio NE, Yeragani VK, Moore NC: Buspirone-induced jitteriness in three patients with panic disorder and one patient with generalized anxiety disorder. *J Clin Psychiatry* 1988; 49: 165-166
6. Eison AS, Eison MS, Riblet LA, et al: Indications of serotonergic involvement in the actions of a potential non-benzodiazepine anxiolytic: MJ 13805. *Neurosciences Abstracts* 1983; 9:436
7. Feighner J: Buspirone in the treatment of anxiety with associated depressive symptoms. *Internal Medicine for the Specialist* 1987; special issue, pp 14-20
8. Schweizer EE, Amsterdam J, Rickels K, et al: Open trial of buspirone in the treatment of major depressive disorder. *Psychopharmacol Bull* 1986; 22:183-185
9. Sanghera MK, McMillen BA, German DC: Buspirone, a non-benzodiazepine anxiolytic, increases locus coeruleus noradrenergic neuronal activity. *Eur J Pharmacol* 1985; 86:107-110
10. Moskowitz H, Smiley A: Effects of chronically administered buspirone and diazepam on driving-related skills performance. *J Clin Psychiatry* 1982; 43(12, section 2):45-55



Plasma Lipid Levels in Patients With Panic Disorder or Agoraphobia

Chris Hayward, M.D., M.P.H., C. Barr Taylor, M.D., Walton T. Roth, M.D., Roy King, M.D., Ph.D., and W. Stewart Agras, M.D.

Plasma lipids were measured in 102 subjects with panic disorder or agoraphobia. In women, but not men, a significantly higher than expected number of subjects had cholesterol values that exceeded the 75th percentile of national reference values for their sex and age.

(Am J Psychiatry 1989; 146:917-919)

A high blood cholesterol level is a major risk factor for the development of cardiovascular disease. The assessment of blood cholesterol levels in psychiatric patients has received little research attention. In particular, there are reasons to suspect that patients with panic attacks might have higher than expected lipid levels. Many studies (1) have demonstrated that acute emotional arousal increases free fatty acids and, in some cases, cholesterol levels. In addition, male patients with panic disorder have been reported to have higher than expected rates of mortality from diseases of the circulatory system (2, 3). The studies yielding these findings had methodologic limitations, such as small sample size and retrospective case identification. Nevertheless, one possible explanation for these findings is high blood cholesterol levels in patients with panic disorder. To test whether patients with panic attacks have high blood cholesterol levels, we measured plasma lipids in 102 patients with panic disorder or agoraphobia and compared them with national reference values.

METHOD

Patients were recruited to participate in two separate treatment trials, one for panic disorder and another for agoraphobia. Patients were required to meet the *DSM-III* criteria for panic disorder or agoraphobia with extensive phobic limitation in order to participate in the treatment studies. The diagnoses were made with the Structured Clinical Interview for *DSM-III*, Upjohn version (4). The exclusion criteria have been reported elsewhere (5). Informed consent was obtained after the procedures had been fully explained.

Plasma lipid values were determined for 102 subjects, 74 women and 28 men. The mean ages (and age ranges) for the women and men were 35.4 (21-55) and 36.4 (19-62) years, respectively. Eighty-four subjects met the *DSM-III* criteria for panic disorder, and 18 subjects had agoraphobia with panic attacks.

Plasma cholesterol and triglycerides were measured by means of enzymatic procedures adapted to the Abbott ABA-200 Bichromatic Analyzer (Irving, Tex.). High-density lipoprotein (HDL) cholesterol was measured after precipitation of other lipoproteins with dextran sulfate magnesium (6). All these measurements were made during "in control" runs, as monitored by the Lipid Standardization Program of the Centers for Disease Control and the National Heart, Lung, and Blood Institute. Low-density lipoprotein (LDL) cholesterol was calculated according to the method of Friedewald et al. (7). Blood samples were drawn after a night of fasting for the 84 subjects with panic disorder, and nonfasting samples were obtained from the 18 subjects with agoraphobia. To assess whether the results were altered by including subjects who had not fasted before venipuncture, we analyzed the data with and without these 18 subjects. The results did not differ in the two analyses. The subjects' levels of total cholesterol, LDL, HDL, and triglycerides were compared with the Lipid Research Clinics Program reference values, which are grouped by age and sex (8). Because of the known effect of sex hormones on lipid levels, the lipid values for the women taking sex hormones (N=12) were compared with the Lipid Research Clinics Program reference values for women using sex hormones (8). In accordance with the guidelines of the National Institutes of Health Consensus

Received Feb. 12, 1988; revision received Dec. 7, 1988; accepted Jan. 19, 1989. From the Laboratory of Behavioral Medicine, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine. Address reprint requests to Dr. Hayward, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305-5490.

Supported by NIMH grant MH-40118, NIMH grant MH-16744, grant HL-07034 from the National Heart, Lung, and Blood Institute, and a grant from the Upjohn Company.

The authors thank H. Kraemer for her statistical consultation and J. Sherman, S. Davies, and K. Murphy for their technical assistance with this study.

Copyright © 1989 American Psychiatric Association.



TABLE 1. Serum Lipid Levels and Prevalence of Greater Risk of Cardiovascular Disease^a In Patients With Panic Disorder or Agoraphobia With Panic Attacks

Measure	Lipid Level (mg/dl)		Patients With Levels Indicating Greater Risk of Cardiovascular Disease ^a			
	Mean	SD	Expected		Observed	
			N	%	N	%
Women (N=74)						
Triglycerides	87	58	18.5	25	12	17
Total cholesterol	208	37	18.5	25	34 ^b	46
LDL cholesterol	133	32	18.5	25	32 ^c	43
HDL cholesterol	58	15	18.5	25	14	18
Men (N=28)						
Triglycerides	149	130	7.0	25	9	32
Total cholesterol	202	38	7.0	25	9	32
LDL cholesterol	132	36	7.0	25	6	21
HDL cholesterol	41	9	7.0	25	11	39

^aLevel of risk based on Lipid Research Clinics Program reference values (8), which are grouped by age and sex. For triglycerides, total cholesterol, and LDL, greater risk=level above 75th percentile. For HDL, greater risk=level below 25th percentile.

^b $\chi^2=17.3$, $df=1$, $p<0.01$.

^c $\chi^2=13.1$, $df=1$, $p<0.01$.

Conference on lowering cholesterol (9), cholesterol values that exceeded the 75th percentile for age and sex were identified as associated with greater risk of developing cardiovascular disease. Similarly, values of LDL and triglycerides above the 75th percentile and values of HDL below the 25th percentile were defined as being associated with such risk. The observed versus expected numbers of subjects with risk-associated values were compared by means of the chi-square statistic.

RESULTS

The lipid values of the female and male patients are shown in table 1. Also shown are the percentages of patients with values associated with greater risk of developing cardiovascular disease. A greater than expected number of female subjects had total cholesterol and LDL values that exceeded the 75th percentile of the national reference values for their age and sex ($\chi^2=17.3$, $df=1$, $p<0.01$ for total cholesterol; $\chi^2=13.1$, $df=1$, $p<0.01$ for LDL). There were no statistically significant findings for triglycerides or HDL in the women and no statistically significant findings for any lipids in the male sample. There was a trend for the male patients to have lower than expected HDL levels ($\chi^2=3.0$, $df=1$, $p<0.1$).

DISCUSSION

In our study, a greater than expected number of women, but not men, with panic disorder or agoraphobia had cholesterol values that exceeded predicted levels, possibly placing them at greater risk for the development of cardiovascular disease. The sex differ-

ences in this study were not as anticipated, since a higher than expected cardiovascular mortality rate has been reported only for men with panic disorder (2, 3). However, the small sample size for men may have limited our ability to detect real differences.

Total cholesterol includes both LDL and HDL subfractions. In this study, 43% of the female subjects had LDL values that exceeded the 75th percentile, but only 20% had HDL values exceeding the 75th percentile. Thus, the LDL subfraction contributed more to the higher than expected total cholesterol level. LDL is positively associated, whereas HDL is negatively associated, with the development of cardiovascular disease.

Diet and exercise patterns can affect body weight, which is positively associated with cholesterol level. To test the possibility that differences in body weight contributed to these findings, we compared the mean body mass index (weight in kilograms divided by height in meters squared) of the female patients with panic disorder (N=59) with that of a female control sample of similar age (N=42, mean age=36.5 years). There was no significant difference in body mass index between the two groups (two-tailed *t* test).

To examine whether prior use of psychotropic medication could have altered lipid metabolism, we re-measured the lipids of the panic disorder patients who completed an 8-week medication trial. There were no statistically significant changes in any lipids after treatment with imipramine, alprazolam, or placebo (Taylor et al., unpublished manuscript).

A possible mechanism for the findings in this study involves the sympathetic nervous system. Sympathetic activation increases the activity of lipoprotein lipase. This results in an increase of free fatty acids in the serum. Theoretically, the hypothesized alteration in adrenergic function observed in patients with panic disorder (10) could alter lipid metabolism by affecting sympathetic regulation of lipoprotein lipase activity. If this were the case, total cholesterol and LDL might be expected to correlate with pertinent clinical variables. To test this possibility, total cholesterol and LDL in women were each correlated with the frequency of panic attacks, score on the Hamilton Rating Scale for Anxiety, score on the Beck Depression Inventory, and a measure of phobic avoidance. The frequency of panic attacks was significantly correlated with total cholesterol level (Spearman correlation, $r_s=0.25$, $N=66$, $p<0.05$). Although this correlation suggests a relationship between panic attack frequency and total cholesterol, the correlation coefficient is not large and represents the only significant correlation of eight correlation analyses performed.

Finally, the higher than expected values of total cholesterol and LDL cholesterol in the female patients highlight the importance of attending to cardiovascular risk factors in psychiatric patients. Patients with panic disorder and agoraphobia should be strongly encouraged to receive cholesterol screening, now recommended for all adults.

REFERENCES

1. Dimsdale JE, Herd JA: Variability of plasma lipids in response to emotional arousal. *Psychosom Med* 1982; 44:413-430
2. Coryell W, Noyes R, Clancy J: Excess mortality in panic disorder: a comparison with primary unipolar depression. *Arch Gen Psychiatry* 1982; 39:701-703
3. Coryell W, Noyes R Jr, House JD: Mortality among outpatients with anxiety disorders. *Am J Psychiatry* 1986; 143:508-510
4. Spitzer RL, Williams JB: Structured Clinical Interview for DSM-III. New York, New York State Psychiatric Institute, 1983
5. Taylor CB, King R, Ehlers A, et al: Treadmill exercise test and ambulatory measures in panic attacks. *Am J Cardiol* 1987; 60: 48J-52J
6. Warnick GR, Benderson J, Albers JJ: Dextran sulfate Mg^{2+} precipitation procedure for quantification of high-density lipoprotein cholesterol. *Clin Chem* 1982; 28:1379-1388
7. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; 18:499-502
8. The Lipid Research Clinics Population Studies Data Book, vol 1: NIH Publication 80-1527. Washington, DC, National Heart, Lung and Blood Institute, Division of Heart and Vascular Diseases, Lipid Metabolism Branch, July 1980, pp 22-81
9. National Institutes of Health Consensus Conference: Lowering blood cholesterol to prevent heart disease. *JAMA* 1985; 253: 2080-2086
10. Neese RM, Cameron OG, Curtis GC, et al: Adrenergic function in patients with panic anxiety. *Arch Gen Psychiatry* 1984; 41: 771-776

Late-Life Onset of Panic Disorder With Agoraphobia in Three Patients

Daniel J. Luchins, M.D., and Robert P. Rose, M.D., Ph.D.

Although the onset of panic disorder with agoraphobia is usually thought to occur in early adulthood, the authors describe three cases in which onset occurred after age 65.

(Am J Psychiatry 1989; 146:920-921)

Agoraphobia is less prevalent in the elderly than in younger adults (1) and is thought to usually first appear in young adulthood. Thorpe and Burns (2) reviewed eight studies and noted that the mean age at onset lay between 19 and 32 years. In their own series of almost 1,000 cases, the mean age at onset was 28, and in only 13% of the cases had onset occurred after age 40. We therefore have been surprised by our own experience over the last 2 years in the geriatric psychiatric service of the Windermere Senior Health Clinic at the University of Chicago. We have noted six cases of agoraphobia and panic attacks in a sample of 126 consecutively evaluated patients (5%), and three of them (50%) had begun after age 65. Because of the presumed rarity of these cases and the relatively few studies of this issue (3), we will present the cases in some detail.

CASE REPORTS

Case 1. Ms. A, a 75-year-old white widow, had a 3-month history of waking at night two or three times a week with anxiety, tachycardia, sweating, weakness, and a sense of claustrophobia, which would persist for 1-2 hours and prevent her from returning to sleep. The episodes appeared to have begun around the time she was bedridden because of sciatica. Now, despite an improvement in her leg pain, she found she had markedly restricted her activities, could not shop or socialize, and required the presence of another individual at all times. To meet this need, a companion was eventually hired by her overburdened family.

She denied depression, other sleep disturbances, guilt, or

change of appetite (although she had lost 30 lb during the previous year, which she ascribed to reflux esophagitis). She reported that she had no previous psychiatric history. She had received no psychotropic medication before being seen at our clinic but was taking a methyldopa-thiazide combination for hypertension, which was continued throughout the subsequent treatment of her psychiatric symptoms.

Ms. A was given desipramine, 25 mg t.i.d., which was increased over 1 month to 50 mg t.i.d. (serum concentration=144 ng/ml), and she was seen weekly by a social worker for psychotherapy, which dealt primarily with which relative she should live near. Within 2 months she experienced dramatic improvement, no longer experienced nighttime panic attacks, was traveling and shopping alone, and no longer required a companion. She was also able to decide to leave the state to live near one of her children.

Case 2. Ms. B, a 75-year-old married white woman, was referred from the cardiology clinic, where she had had an extensive workup and had been given a diagnosis of mild mitral valve prolapse. She had a 6-month history of almost nightly episodes of waking with chest pain, tachycardia, anxiety, and fear of dying, which prevented her from returning to sleep for 45-60 minutes. These episodes had started a few days after her husband coerced her into flying with him in a small private plane, an experience she found terrifying. Aside from the nighttime episodes, she also described feeling anxious and dizzy in certain situations, such as being in a crowded shopping mall alone, which did not happen when her husband accompanied her. Ms. B also described a 2-year history of mild depression associated with concerns about being old and having little to look forward to. This depression had intensified in the last 6 months because of her impending retirement. She had experienced no changes in appetite, weight, or sleep and no episodes of crying or suicidal ideas. She reported an episode of significant depression at age 41, after her first husband's death, but no previous panic attacks or agoraphobic symptoms.

Ms. B had used diazepam, 2.5 mg as needed, for about 10 years, but it did not alleviate her panic attacks. She did note that during these episodes lorazepam, 1 mg as needed, reduced the chest pain and helped her return to sleep. She was treated with alprazolam, 0.25 mg b.i.d., which reduced the frequency of panic attacks to about one every 2-3 weeks and relieved her fear of crowded situations. During treatment Ms. B retired and experienced no exacerbation of symptoms.

Case 3. Ms. C, an 89-year-old white widow, had a 2-year history of almost daily "dizzy spells" associated with intense anxiety, shortness of breath, tremor, sweating, and lightheadedness. These episodes could occur spontaneously but were inevitable if she entered a crowd or had to stand in line,

Received Aug. 16, 1988; revision received Jan. 11, 1989; accepted Jan. 13, 1989. From the Section of Geriatric Psychiatry, Department of Psychiatry, Pritzker School of Medicine, University of Chicago; and the Illinois State Psychiatric Institute, Chicago. Address reprint requests to Dr. Luchins, Department of Psychiatry, University of Chicago, 5841 S. Maryland Ave., Chicago, IL 60637.

Copyright © 1989 American Psychiatric Association.

which limited her ability to leave home. According to Ms. C's family, these symptoms and her increasing social isolation started after a difficult hospitalization, during which she was immobilized by sciatica. When we first saw Ms. C, she was receiving no medication. She admitted being depressed because of the attacks and having some initial insomnia, although she still slept 6–10 hours each night. She had a normal appetite and desire to carry out activities. She reported no feelings of guilt or suicidal ideas. She had no previous history of panic attacks or significant depression except for a 3-month period of grieving for her husband, who had died about 20 years previously. In addition, she had experienced decreased cognitive function for at least 2 years; examination revealed occasional paraphasias, the ability to remember only two of three objects, and a score of 6 out of 10 on the Mental Status Questionnaire (4). A CT scan had previously revealed several small subcortical infarcts. Her cognitive decline was attributed to a multi-infarct dementia. She was given alprazolam, 0.25 mg b.i.d., for her panic attacks with agoraphobia but was lost to follow-up.

DISCUSSION

Before it is concluded that these three cases are examples of late-onset panic attacks and agoraphobia, several issues should be addressed. First, these cases were not collected in the context of a systematic research study. The information is retrospective and may be limited by both the patients' recollections and the physician's persistence. Nevertheless, in all cases, the patients considered the panic attacks as new developments and the individuals had limited or no previous psychiatric histories. The second issue is differential diagnosis. Marks (5) suggested that when agoraphobia starts in middle age or later, the diagnoses of space phobia and depression need to be excluded. The clinical pictures of these individuals do not resemble space phobia, which is characterized by an intense fear of

falling in open spaces without visual support. On the other hand, two of the three patients could be said to have mild depressive symptoms, and the patient in case 2 probably would meet the *DSM-III-R* criteria for dysthymic disorder. None, however, met criteria for a major depression. In any case, current or previous depression is found in about two-thirds of agoraphobic patients (6). Attempts to differentiate cases in which the depression is primary from those in which agoraphobia predominates have been fruitless, since, as Marks (5) noted, "The similarities were more impressive than the differences."

Assuming that these three individuals developed bona fide panic disorder with agoraphobia in their late years, what can we learn from these cases? Primarily that this condition can have a late onset and must be considered in the differential diagnoses of individuals in that age range. A higher index of suspicion for onset of this condition in the elderly might reduce the possibility of ascribing panic symptoms and the reductions of activity associated with agoraphobia to medical conditions, which are frequent in this age group.

REFERENCES

1. Myers JK, Weissman MM, Tischler GL, et al: Six-month prevalence of psychiatric disorders in three communities, 1980 to 1982. *Arch Gen Psychiatry* 1984; 41:959–967
2. Thorpe GL, Burns LE: *The Agoraphobia Syndrome*. New York, John Wiley & Sons, 1983
3. Sheikh JI, Taylor CB, King RJ, et al: Panic attacks and avoidance behavior in the elderly, in CME Syllabus and Scientific Proceedings in Summary Form, 141st Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1988
4. Kahn RL, Goldfarb AI, Pollack M, et al: Brief objective measures for the determination of mental status in the aged. *Am J Psychiatry* 1960; 117:326–328
5. Marks IM: *Fears, Phobias, and Rituals: Panic, Anxiety, and Their Disorders*. New York, Oxford University Press, 1987
6. Breier A, Charney DS, Heninger GR: Major depression in patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 1984; 41:1129–1135

Three Cases of Panic Disorder With Agoraphobia in Children

James C. Ballenger, M.D., Donald J. Carek, M.D., Jane J. Steele, M.S.W.,
and Denise Cornish-McTighe, M.D.

The authors report three cases of panic disorder with agoraphobia in children, with characteristic panic attacks, separation anxiety, and fear and avoidance of crowds and public places. The panic and agoraphobic symptoms responded to medications effective with agoraphobic adults, i.e., imipramine and alprazolam.

(Am J Psychiatry 1989; 146:922-924)

It is increasingly apparent that psychiatric illnesses previously thought to be specific to adulthood can begin in childhood (1-3). Anxiety disorders such as panic disorder and agoraphobia are rarely diagnosed in children, although the diagnosis of separation anxiety is commonly made. Even though there is evidence that panic disorder and agoraphobia are familial (4, 5) and many agoraphobic adults retrospectively report symptoms as children, few clinicians or investigators have studied these disorders in children (6-8). We report here three children with typical panic attacks and agoraphobic fears and avoidance in an effort to stimulate further discussion of the childhood form of panic disorder.

CASE REPORTS

Case 1. Ann, 8 years old, presented with a 6-month history of abdominal pain and nonspecific fear that occurred in crowded places. Ann avoided school activities and family outings because of her fear of going into crowded areas. On one occasion when on a trip with her family, she ran out of a building after she experienced a panic attack in a cafeteria line. Panic attacks, accompanied by shortness of breath, palpitations, abdominal pain, and a feeling of being "out of control," occurred as often as twice a day, especially when she was away from the home. Ann frequently called from

school, asking to be taken home, and protested when she was encouraged to attend activities with peers away from the home. Her abdominal pain and unwillingness to eat in the cafeteria at school led to a 5-lb weight loss in 3 months. She denied feelings of depression, worthlessness, or hopelessness. Her panic attacks and persistent fear of having more attacks would have met adult criteria (DSM-III-R) for panic disorder with agoraphobia of moderate severity. Ann's mother, successfully treated with alprazolam for panic disorder with extensive phobic avoidance (DSM-III-R), felt that her daughter's symptoms paralleled her own and brought her for treatment.

Treatment with alprazolam, in combination with imipramine for almost a year, resulted in complete remission of symptoms. Alprazolam was tapered and discontinued easily, and Ann was treated with imipramine (75 mg at bedtime) alone for 2 additional years. She was seen in individual supportive psychotherapy every 1 to 2 weeks during most of this time. When imipramine was discontinued she developed transient somatic symptoms, but these cleared and she did well. However, 5 months after imipramine was discontinued she experienced a full relapse, was retreated with imipramine (75 mg/day), and recovered in several weeks. After an additional 2 years of successful drug treatment and supportive psychotherapy, medication was tapered and discontinued at the end of a school year. Ann did well initially but began having spontaneous panic attacks approximately 5 months later, after returning to the stress of school. Imipramine treatment was restarted, and there was complete improvement of symptoms with 75 mg/day. Supportive psychotherapy and family sessions, as well as simple relaxation techniques, were included as adjuncts to drug treatment. Ten months later Ann continued to take the medication, the frequency of supportive psychotherapy sessions had decreased, and she remained symptom free despite major stressors within her family. Medication taper was again planned at the end of the school year.

Case 2. Alan, 13 years old, developed the fear that he would faint in school or other public places after having felt faint in the lunch line at school. He began to experience sudden episodes of palpitations and increased perspiration accompanied by the fear that he would faint or "lose control" in class, the mall, or church. At those times he was noted to look pale and to feel cold and "clammy." Examination by a cardiologist resulted in the diagnosis of mitral valve prolapse, but this was not felt to account for his symptoms. Because of his attacks, Alan avoided crowds, especially in malls and large school functions. He would attend church services only if he could sit in the back of church so that he

Received May 3, 1985; revisions received April 25, 1988, and Jan. 11, 1989; accepted Feb. 2, 1989. From the Department of Psychiatry and Behavioral Sciences and the Institute of Psychiatry, Medical University of South Carolina. Address reprint requests to Dr. Ballenger, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 171 Ashley Ave., Charleston, SC 29425.

Copyright © 1989 American Psychiatric Association.

could leave quickly if he became anxious. He met adult criteria (*DSM-III-R*) for panic disorder with agoraphobia of moderate severity.

Alan was treated with alprazolam, 1.0 mg twice daily, and imipramine, 125 mg at bedtime, and experienced complete remission of his symptoms. After 4 months alprazolam was reduced to 0.5 mg twice a day. After 8 months alprazolam was tapered and discontinued without reappearance of symptoms, and imipramine was reduced to 75 mg/day. Imipramine was discontinued after a total of 12 months of treatment without return of symptoms.

Alan was seen in psychotherapy a total of 14 times over the initial 7 months. An attempt was made to engage him in reflective psychotherapy, but this was largely unsuccessful. Over the next 6 months he was seen four times to determine "how things were going," for general support, and to check on his medications. It was our impression that his improvement was primarily related to the medications.

Case 3. Cathy, 11 years old, had always had a problem with separation, avoided sleep-over parties, and disliked it when her parents went out. She began having abdominal pain when she changed to a new school. Several visits to her pediatrician resulted in no diagnosis, and an upper gastrointestinal series was normal. While in school, she began to have spontaneous panic attacks that were characterized by the sudden feeling that she was going to die, trembling, sweaty hands, tingling in her legs, and dizziness. Afterward, she worried that "something might happen to me." Although Cathy had been active and independent during the summer, after school began she spent less time with friends and did not want to be left alone. Consequently, she often accompanied her mother on errands but would have panic attacks in stores. She called her mother frequently from school, asking to be taken home. She met adult criteria (*DSM-III-R*) for panic disorder with agoraphobia of mild severity. Cathy was awakened at night by abdominal pain and lost 5 lb. She denied feeling sad or worthless. The only family history of psychiatric problems was depression in her maternal grandmother.

Cathy was treated successfully with 75 mg/day of imipramine, which effectively blocked her panic attacks. Despite occasional complaints of stomachaches when she was under stress, she returned to activities she had been avoiding. Sessions with the patient and her parents provided education about anxiety disorders and focused on helping the parents encourage appropriate separation. Imipramine was tapered after 2 years, and there was no known relapse over 27 months.

DISCUSSION

There is a relative dearth of information and clinical investigation concerning panic disorder and agoraphobia in childhood, although Gittelman-Klein and Klein first suggested in 1973 that separation anxiety in childhood was closely related to adult agoraphobia (9, 10). The children we have described met adult criteria (*DSM-III-R*) for panic disorder with varying degrees of agoraphobia. Although we did not use structured diagnostic interviews with these children, we came to know them well through extensive clinical contact, generally over several years. Although they had fea-

tures of separation, avoidant, and phobic disorders of childhood, their clinical syndromes appeared very similar to the usual adult presentation of panic disorder, and we feel it is most appropriate to conceptualize them as having the same syndrome. This conclusion is further supported by the fact that they appeared to respond to treatment "like adults" (e.g., to the same medications).

There are several reasons why the presence of panic disorder and agoraphobia in children may be underappreciated, other than the belief that they do not occur until early adulthood. Avoidant behavior in children may be more difficult to recognize because children are protected and dependent and underlying anxiety may remain unchallenged and therefore unexposed. There is a relatively greater diagnostic awareness of depression in children than of anxiety. A child's tearful, sad, forlorn appearance may distract examiners from the underlying anxiety that becomes evident only on closer scrutiny. In addition, children may be even more prone than adults to emphasize their physical symptoms (e.g., cases 1 and 3) over their anxiety and avoidance symptoms. Correct recognition of this disorder in children is probably quite important because it would better allow early detection and intervention, which should help prevent the patterns of chronic avoidance and lowered self-esteem that individuals with untreated panic disorder frequently develop.

These three children responded to treatment with resolution of their panic and avoidance symptoms and with resumption of age-appropriate activities. Although each of the children was seen in psychotherapy by psychotherapy-oriented clinicians, there was clear consensus among us that symptom resolution was primarily related to the medications. This impression was based on both the time course of symptom resolution and the two relapses in patient 1 when medication was discontinued and the subsequent good responses when medication was reinstituted.

Obviously, many of the issues raised by this preliminary report now require rigorous study. However, it is our hope that our description of the symptom patterns and successful treatment of these children will stimulate others to explore the nature of these symptoms and this disorder in children.

REFERENCES

1. Cytryn L, McKnew DH Jr, Bartko JJ, et al: Offspring of patients with affective disorders, II. *J Am Acad Child Psychiatry* 1982; 21:389-391
2. Beardslee WR, Bemporad J, Keller MB, et al: Children of parents with major affective disorder: a review. *Am J Psychiatry* 1983; 140:825-832
3. Rapoport JL: *The Boy Who Couldn't Stop Washing: The Experience and Treatment of Obsessive-Compulsive Disorder*. New York, EP Dutton, 1989
4. Crowe RR, Noyes R, Pauls DL, et al: A family study of panic disorder. *Arch Gen Psychiatry* 1983; 40:1065-1069

CLINICAL AND RESEARCH REPORTS

5. Harris EL, Noyes R, Crowe RR, et al: Family study of agoraphobia: report of a pilot study. *Arch Gen Psychiatry* 1983; 40:1061-1064
6. Berg I: School phobia in children of agoraphobic women. *Br J Psychiatry* 1967; 128:86-89
7. Weissman MM, Leckman JF, Meukanjos KR, et al: Depression and anxiety disorders in parents and children. *Arch Gen Psychiatry* 1984; 41:845-852
8. VanWinter JT, Stickler GB: Panic attack syndrome. *J Pediatr* 1984; 105:661-665
9. Gittelman-Klein R, Klein D: School phobia: diagnostic considerations in light of imipramine effects. *J Nerv Ment Dis* 1973; 156:199-215
10. Gittelman-Klein R: Pharmacotherapy and management of pathological separation anxiety. *Int J Ment Health* 1975-1976; 4: 255-271

Midazolam for Aggressivity and Violence in Three Mentally Retarded Patients

William S. Bond, Pharm.D., Laura A. Mandos, Pharm.D., and Michael B. Kurtz, M.D.

Midazolam was administered to three mentally retarded patients with acute and refractory aggressivity and violence. Midazolam was well tolerated without complications and provided dramatic control of the symptoms, suggesting an expanded role for it in the management of aggressive and violent behavior.

(Am J Psychiatry 1989; 146:925-926)

Clinically significant behavior related to assaultiveness and violence (e.g., anger and agitation) is common among psychiatric patients (1). Violent behavior is unpredictable and periodic and adds disproportionate severity to any environmental stress or frustration (2).

In patients with mental retardation, violent and aggressive behavior is often coupled with self-injurious acts such as head banging and self-mutilation (3, 4). The presence of such symptoms, of course, greatly complicates the management of mentally retarded patients and, in extreme cases, can stymie attempts at adequate control.

The use of psychotropic medications to manage behavior disorders in patients with mental retardation is controversial. Pharmacotherapy has become a symbol of the failure of many institutions to provide meaningful rehabilitation services to the mentally retarded. This view has evolved because drug therapy has been used as a chemical restraint in some clinical situations to the exclusion of a well-planned behavior modification program (5). Unfortunately, this often deserved criticism has obscured the fact that there are extremely disturbed retarded individuals who cannot benefit from any type of rehabilitation program unless they are adequately medicated.

Acute episodes of aggressivity and lack of control require rapid measures to minimize disruption to the milieu and to prevent patients from harming themselves and others. Although parenteral antipsychotic

drugs remain the mainstay of treatment, patients may obtain incomplete or inadequate relief and suffer disturbing drug-induced adverse effects such as orthostatic hypotension and extrapyramidal reactions. Benzodiazepines used in combination with antipsychotic drugs or as alternative agents can help overcome these problems.

Midazolam, a [1, 4]benzodiazepine derivative currently used as a parenteral preanesthetic, is a particularly suitable drug for this purpose because of its pharmacologic and pharmacokinetic properties. Midazolam is a highly lipophilic drug at physiologic pH, which contributes to the rapid onset of its CNS effects. The sedative effects of the drug begin within 5 to 15 minutes after intramuscular administration, and peak sedation occurs 30 to 60 minutes following intramuscular injection. The onset of sedation is even more rapid (within 3 to 5 minutes) after intravenous injection. The rapid displacement of midazolam from benzodiazepine receptors and its very high metabolic clearance and high rate of elimination account for its relatively short duration of action, which is about 2 hours (range=1-6 hours).

Overall, midazolam is remarkably free from adverse effects. The incidence of apnea and postoperative emergence delirium, nausea, and vomiting is relatively low following midazolam administration compared with other anesthetic agents. Compared with thiopental, it causes less cardiorespiratory depression and a lower frequency of coughing, hiccups, laryngospasm, and bronchospasm. Midazolam may prove to be particularly useful as an alternative agent in patients with cardiac disease, geriatric patients, and patients who cannot tolerate intravenous barbiturates or for whom they are contraindicated.

Midazolam generally causes less pain and venous irritation at the site of injection than diazepam or hydroxyzine. In addition, midazolam has a more rapid onset of sedative action and produces more pronounced anxiolytic and anterograde amnesic effects than parenteral diazepam or hydroxyzine (6, 7).

The properties that make midazolam a safe and effective preanesthetic agent also would be useful in the management of psychiatric patients with aggressive and violent behavior. This hypothesis is supported by a recent report by Mendoza et al. (8), who provided the first data concerning the efficacy of intramuscular

Received May 31, 1988; revision received Nov. 22, 1988; accepted Dec. 30, 1988. From the Philadelphia College of Pharmacy and Science and the University of Pennsylvania, Philadelphia. Address reprint requests to Dr. Bond, Philadelphia College of Pharmacy and Science, Woodland Ave. at 43rd St., Philadelphia, PA 19104. Copyright © 1989 American Psychiatric Association.

midazolam for the treatment of acutely psychotic patients in an emergency room setting.

Our favorable clinical experience with intramuscular midazolam not only supports the findings of Mendoza et al. but extends them to include midazolam's efficacy in individuals with mental retardation coexisting with other psychiatric illness who manifest resistant and severe forms of violence and agitation. In the cases of each of the three patients described here, a planned behavior modification program was in place as part of the overall therapy. No adverse drug effects were experienced by any of the patients, and their vital signs remained stable after injection of midazolam.

CASE REPORTS

Case 1. Anthony is a 17-year-old boy with the psychiatric diagnoses of mild mental retardation (IQ=60), impulse control disorder, and attention deficit disorder with hyperactivity. His pharmacotherapy included maintenance methylphenidate (60 mg/day) as well as thioridazine (300 mg/day) and hydroxyzine (10 mg i.m. as needed) for agitation and behavior control. Despite these medications, Anthony continued to experience episodes of agitation, destructive behavior, and violence during which he would pull down window drapes, pull fire alarms, rip his clothing, and physically assault staff and other patients. A trial of lithium carbonate (1200 mg/day) proved ineffective in reducing the number and severity of these episodes and appeared to worsen his behavior of inappropriate urination. Positive reinforcement programs and periods of "time out" also were ineffective.

Because of the lack of effect of both pharmacotherapy and nonsomatic treatments, Anthony was given 5 mg of midazolam on several occasions of severe agitation and violence. On each occasion it produced dramatic control of his aggressivity within 10 to 20 minutes following injection. Usually, he would sleep for about 60 minutes after the injection and was much more manageable on awakening and able to participate in milieu activities.

Case 2. Betty is a 14-year-old girl with psychiatric diagnoses of mild mental retardation (IQ=69); conduct disorder, socialized, aggressive type; and explosive personality disorder. She was extremely noncompliant and would often be severely aggressive and violent toward both herself and the staff. Therapy with lithium carbonate (1125 mg/day) and as-needed parenteral administration of triflupromazine (25 mg) and sodium amobarbital (100–200 mg) for acute episodes of severe agitation were ineffective.

During one of her acute episodes, Betty attempted to hit staff members with a chair and exhibited self-abusive head banging during a "time-out" period in an open seclusion room. She was given 10 mg of midazolam, which produced

rapid control of her aggressive and violent symptoms. Betty was able to come out of the room within 15 minutes following the injection and was subsequently alert and cooperative with the staff's directions.

Case 3. Mr. C is a 26-year-old man with severe mental retardation (IQ=29) and a mixed seizure disorder treated with phenobarbital (120 mg/day). He was usually compliant but infrequently would exhibit episodes of temper tantrums and severe agitation that were difficult to control. Although intramuscular triflupromazine (20–25 mg) was somewhat effective, it had to be discontinued because the patient experienced prolonged periods of lethargy following its use. Substitution of parenteral hydroxyzine (50–150 mg) proved to be ineffective.

Over a period of about 8 months the patient had three documented episodes of severe agitation and self-abusive behavior unresponsive to "time-out" periods and restraints. However, on each occasion, administration of 10 mg of midazolam produced rapid control of his symptoms—usually within 15 to 20 minutes following the injection. He then was able to resume participation in his usual daily activities.

These three case reports illustrate the safety and efficacy of midazolam in the management of mentally retarded individuals with acute episodes of severe aggressivity and violence unresponsive to other psychotropic drugs and behavioral measures. Its sedative, anxiolytic, and amnesic effects likely account for its usefulness in these patients. However, double-blind controlled studies of midazolam used with and without antipsychotic drugs are required to confirm its utility in patients with violent behavior.

REFERENCES

1. Craig TJ: An epidemiologic study of problems associated with violence among psychiatric inpatients. *Am J Psychiatry* 1982; 139:1262–1266
2. Linn L: Clinical manifestations of psychiatric disorders, in *Comprehensive Textbook of Psychiatry*, 4th ed, vol 1. Edited by Kaplan HI, Sadock BJ. Baltimore, Williams & Wilkins, 1985
3. Ando H, Yoshimura I: Prevalence of maladaptive behavior in retarded children as a function of IQ and age. *J Abnorm Child Psychol* 1978; 6:345–349
4. Maistro C: An analysis of variables related to self-injurious behavior among institutionalized retarded persons. *Ment Defic Res* 1978; 22:27–36
5. Plotkin R, Gill KR: Invisible manacles: drugging mentally retarded people. *Stanford Law Rev* 1979; 31:637–678
6. Kanto JH: Midazolam: the first water-soluble benzodiazepine. *Pharmacotherapy* 1985; 5:138–155
7. McEvoy GK (ed): *American Hospital Formulary Service Drug Information* 88. Bethesda, Md, American Society of Hospital Pharmacists, 1988
8. Mendoza R, Djenderedjian AH, Adams J, et al: Midazolam in acute psychotic patients with hyperarousal. *J Clin Psychiatry* 1987; 48:291–292

Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

TEXTBOOKS

The American Psychiatric Press Textbook of Psychiatry, edited by John A. Talbott, M.D., Robert E. Hales, M.D., and Stuart C. Yudofsky, M.D. Washington, D.C., American Psychiatric Press, 1988, 1,279 pp., \$85.00.

Quite simply, this is the best textbook of psychiatry currently available. It is a textbook in the finest sense of the word in that it is clearly written, comprehensive (but not overwhelming), and unbelievably up-to-date. The editors and contributors are to be congratulated. This book presents the "new psychiatry" in an extremely clear fashion and in one volume. It is apparent that the book was carefully designed and edited to teach. Each chapter is full of excellent summary tables that encapsulate the key didactic messages of the text. Great consideration for the reader has been shown in the effort to make the text and concepts understandable. For example, this is the first basic text I have seen that goes into a brief but clear discussion of statistics used in epidemiologic studies. It is also the first to give examples of the currently available standardized interview schedules. Such consideration allows the reader to understand the terms that are used without having to go to another book to look them up.

The text is divided into five sections: Theoretical Foundations, Assessment, Psychiatric Disorders, Psychiatric Treatments, and Special Topics. The first three chapters in the Theoretical Foundations section, "Neuroscience and Psychiatry" by Joseph T. Coyle, "Genetics" by Ronald O. Rieder and Charles A. Kaufmann, and "Epidemiology of Mental Disorders" by Jack D. Burke, Jr., and Darrel A. Regier, are the clearest chapters on these subjects that I have ever seen. They should be read by all psychiatrists who finished their residencies more than 5 years ago. These chapters should stimulate the intellectual interests of medical students and residents by demonstrating the major advances that have been made in the application of the basic sciences to understanding behavior disorders. "Normal Growth and Development" by Theodore Shapiro and Margaret E. Hertzog is a clear, well-balanced summary of the data on child development. Unfortunately, "Theories of the Mind and Psychopathology" by Stephen S. Marmer is not up to the standards of the preceding chapters in terms of a balanced presentation. It deals primarily with psychoanalytic theory. One is certainly taken aback to find this parochial view after reading the earlier presentations. Certainly one would expect in such a chapter to find data from neuropsychology and reference to such theoreticians as James, Hebb, and Penfield, who have all contributed greatly to our understanding of mental activity. However, it is a good review of psychoanalytic theory.

The section on Assessment is as fine as the first section. It starts with "Psychiatric Interview, Psychiatric History, and Mental Status Examination" by Stephen C. Scheiber, which includes an outline of the examination by Roger A. MacKinnon and Stuart C. Yudofsky. "Psychiatric Classification" by Janet B.W. Williams follows. This first-rate discussion cer-

tainly should be useful in helping medical students understand the importance of diagnosis in psychiatry as well as the contemporary interest in it. Both of these chapters are quite readable, full of examples and clinical illustrations, and not at all like reading a dictionary, as some chapters on this subject are prone to be. "Psychological Assessment: Tests and Rating Scales" by John F. Clarkin and Stephen W. Hurt and "Laboratory and Other Diagnostic Tests in Psychiatry" by Richard B. Rosse and John M. Morihisa are also quite good. In the latter, there is some lack of sophistication in the discussion on distinguishing medical from psychiatric problems; however, the guidelines for clinical evaluation before starting psychopharmacological treatments are excellent and should prove valuable for residents and practicing psychiatrists who are trying to use an unfamiliar medication.

In the Psychiatric Disorders section, the chapters follow *DSM-III-R* closely and are all written by experts in the field. They follow the traditional medical textbook format in giving some historical overview of the diagnostic category and then going on to a clear discussion of definition, epidemiology, clinical features, and treatment. The presentations are vivid, well balanced, and every bit as good as the chapters in the first two sections of the book. The chapters on personality disorders, children, and psychosomatic conditions are extremely comprehensive and well written, but it is difficult to single out one chapter from this excellent overview of psychopathology.

Section four, Psychiatric Treatments, covers such topics as psychopharmacology and ECT, individual psychotherapies, behavior therapy, hypnosis, family therapy, group therapy, and treatment of children and adolescents. "Psychopharmacology and Electroconvulsive Therapy" by Jonathan M. Silver and Stuart C. Yudofsky is organized in an interesting fashion in that it deals with medications according to their functions (e.g., anti-aggressive drugs and antipsychotic drugs) rather than exclusively by their pharmacological classes. "Individual Psychotherapies" by Robert J. Ursano and Edward K. Silberman is very broadly based and ranges from psychoanalysis to short-term therapy. It also covers cognitive therapy, and there is a lovely and detailed discussion of supportive therapy, which is frequently neglected. "Hypnosis" by David Spiegel is first-rate, and "Family Therapy" by C. Christian Beels clears a nice didactic path through a very complex area. "Treatment of Children and Adolescents" by Mina K. Dulcan is comprehensive and useful.

The Special Topics section covers such areas as suicide, violence, psychiatry and the law, ethics and psychiatry, psychiatry and culture, geriatric psychiatry, community psychiatry and prevention, and administration. Although most of the chapters are extremely well done and didactically useful, this section contains two of the weakest chapters in the book. The chapter on psychiatry and culture does not deal in a very comprehensive way with the fascinating area of cross-cultural issues in psychiatry and their implications for psychopathology. The chapter on geriatric psychiatry is superficial about the biological aspects of geriatrics as well as some of

the social issues. It is also a mystery to me why there is a chapter on administration in this excellent textbook. I do not think it is a pertinent issue for most medical students and residents. This is not to deny the importance of administrative functions for residents, but this chapter does not seem to fit with the rest of the book.

There are two appendixes in the text, one covering the diagnostic criteria of *DSM-III-R*, which have already been covered in the Psychiatric Disorders portion of the text, and a second appendix consisting of excerpts from the *American Psychiatric Glossary* (1). The index is quite adequate.

In summary, this text will be useful for medical students and residents and particularly useful for physicians and psychiatrists who have been out of their residency programs for more than 5 years. The chapters on neuroscience and psychiatry, genetics, and epidemiology will be important reviews for most practicing psychiatrists.

It is difficult to review a textbook, so to confirm the usefulness of this book I did a private study. Shortly after receiving the book, I was the attending physician with a first-year resident for a week on one of our inpatient services. During this time, I wrote down specific questions asked by the resident and the medical student that could have been answered by a good textbook. *The American Psychiatric Press Textbook of Psychiatry* was quite good in answering four of the seven questions. The answered questions related to the use of neuroleptics in a patient who was breast feeding, the relationship of the WBC to the use of carbamazepine (although the answer was a bit conservative, as it probably should be, it was accurate), when to stop ECT, and the psychiatric aspects of psoriasis. Unanswered questions involved the topics of postpartum psychosis, atypical depression, and the psychiatric sequelae of head trauma. Although head trauma is covered in the book, it was only in its relation to subsequent violence. In short, the book did a pretty good job in replacing the attending physician, which I think is a sign of an excellent textbook.

I recommend this textbook highly. Both the American Psychiatric Press and the editors and authors certainly can be proud of it.

REFERENCE

1. Stone EM (ed): *American Psychiatric Glossary*, 6th ed. Washington, DC, American Psychiatric Press, 1988

GARY J. TUCKER, M.D.
Seattle, Wash.

Introduction to Psychodynamics: A New Synthesis, by Mardi J. Horowitz. New York, Basic Books, 1988, 272 pp., \$22.95.

The student who wishes to appropriate the riches of psychoanalytic theory faces a formidable task. Not only is the landscape vast, but there is no good map. To make matters worse, the journey is fraught with twists, turns, and dead ends. One can easily get lost or, frustrated and overwhelmed, turn back.

In this book, Mardi J. Horowitz, who has written an influential series of clinical works, sets himself the task of translating psychoanalytic theory into a contemporary idiom that is accessible to the student clinician. While attempting to be faithful to the traditional sources of psychoanalytic theory, Horowitz frames his synthesis with strong contributions

from a number of nonanalytic sources, including cognitive and personality psychology.

Assessment of the adequacy of any new theoretical formulation, especially one that aspires to be comprehensive, can be based on its faithfulness to the received tradition, its clinical and empirical utility, and its conceptual elegance. Brief consideration of these points follows.

Introduction to Psychodynamics maintains fidelity to the received tradition by addressing the traditional viewpoints of psychoanalytic metapsychology: dynamic, structural, economic, genetic, and adaptive (1). The dynamic and structural points of view are strongly represented in the concepts of "schemas" and states of mind. Borrowed from cognitive psychology, schemas of self and other and their associated but more elaborated role relationship models are mental representations composed of images and patterned interactional expectancies. They organize experience and act as focuses for perceptions, thoughts, emotions, and choices. The patterned sequencing of the various states of mind constitutes personality and reflects the many-layered and constantly shifting texture of consciousness, which is the heart of psychodynamic theory. Borrowing heavily from traditional sources, Horowitz articulates developmental processes by which schemas are acquired, hierarchically organized, and reorganized across the life span. Finally, demonstrating his reliance on modern personality psychology, Horowitz's model is strongly interactionist. It takes seriously the notion that human beings exist in a constantly changing and, most importantly for a theory of mental states, salient social environment.

A second consideration for evaluating the adequacy of a new theoretical synthesis is its utility, specifically its value in clinical conceptualization and empirical verification. *Introduction to Psychodynamics* is "experience-near" in its conceptualization: it has recognizable clinical validity and power of illumination. The approach is eminently empirical, lending itself well to the sort of clinical investigation that is likely to characterize the coming decades of psychoanalytic theorizing. Indeed, a major strength of Horowitz's work over the past 20 years is its characteristically strong empirical basis.

Finally, Horowitz's model has the value of conceptual elegance. His framework, which weaves psychoanalytic theory into a general psychology, has the beauty of cohesion, consistency, and clinical validity.

Does Horowitz succeed in translating psychoanalytic theory for a generation of clinicians bred on the psychology of the 1960s and 1970s? He does. This work points beyond itself toward further elaboration and application.

My only complaint, and it is a minor one, is that the book ends prematurely, after a useful section which recasts defense mechanisms and neurotic styles into schema theory. The treatment would have been nicely rounded off by chapters on psychopathology (prototypic schemas and states of mind that organize pathological behavior) and psychotherapy praxis and research. Nevertheless, Horowitz has succeeded in creating a text that conveys, and extends, a venerable clinical heritage for both the psychoanalytic neophyte and the seasoned veteran.

REFERENCE

1. Rapaport D, Gill MM: The points of view and assumptions of metapsychology. *Int J Psychoanal* 1962; 40:153-162

MARVIN W. ACKLIN, PH.D.
Honolulu, Hawaii

Principles and Practice of Child Psychiatry, 2nd ed., by Stella Chess, M.D., and Mahin Hassibi, M.D. New York, Plenum, 1986, 522 pp., \$35.00.

This book offers an updated overview of the field of child psychiatry. Written in an easy-to-read style, it is appropriate for both professionals and interested lay people.

The introductory chapters provide a historical overview of the field as well as chapters on normal child development and theories of child development. The section entitled Disordered Behavior discusses the genesis and etiology as well as the presenting symptoms of disordered behavior and includes an extensive chapter on assessment. The bulk of the text is devoted to the section entitled Syndromes in Child Psychiatry. Case histories are provided throughout. Subjects covered in separate chapters include adjustment reactions, disorders of biological functions (eating disturbances, disorders of sleep, enuresis, encopresis, and psychosexual disorders), psychophysiological disorders, anxiety disorders, childhood psychoses (autism, schizophrenia, affective disorders), learning disabilities, disorders of language development, organic brain syndromes, hyperkinesia and attentional deficiencies, and disorders of habit (including stereotyped movements, self-injurious behavior, and tics). Particularly informative and interesting are the chapters on mental retardation and physically handicapped children. There are also chapters on gifted children and normal and pathological behavior in adolescence. Coverage is relatively weak in the areas of substance abuse and, perhaps reflecting the state of the knowledge at the time the book was written, physical and sexual abuse. The last section of the book, Methods of Psychiatric Intervention, provides brief overviews of psychoanalysis, play therapy, behavior therapy, group therapy, family therapy, compensatory education, institutionalization, and drug therapy. The final chapter is entitled "Children and the Law."

Compared with the first edition, increased coverage has been given in this second edition to child psychopharmacology, learning disabilities, and the role of the school in psychiatry. In addition, as the authors note, the diagnostic terminology has been modified generally to comply with DSM-III.

Although details and research references are sometimes lacking, *Principles and Practice of Child Psychiatry, 2nd ed.*, provides a broad-based overview of an ever-expanding field.

DEANNA BOOK, M.D.
SAMUEL KUPERMAN, M.D.
Iowa City, Iowa

CLINICAL CARE

Diagnosis and Classification in Psychiatry: A Critical Appraisal of DSM-III, edited by Gary L. Tischler. New York, Cambridge University Press, 1987, 546 pp., \$59.50.

Potential readers should not be put off by the fact that this book is largely composed of the proceedings of a 3-day conference held in 1983. The conference was organized by the Board of Trustees of APA to evaluate DSM-III. This book is much more useful than most such proceedings, even though DSM-III has been superseded by DSM-III-R and DSM-IV is already under discussion. DSM-III-R, which was published in 1987, is not fundamentally different from DSM-III, and

much of the debate and discussion contained in this volume about the background of the structure and content of DSM-III still applies to DSM-III-R.

In spite of its subtitle, there is not a great deal of criticism in this volume, although there is a great deal of description and explanation. This may be due to the fact that many of the contributors to the volume were also members of various working parties and task forces that drafted both DSM-III and DSM-III-R. It is a pity that nobody from outside the United States was asked to contribute to this volume, but this is no particular disadvantage so long as DSM-III was not expected to be more than a national classification. There is little mention in this volume of an international role for DSM-III, but time has shown that there has been considerable international interest in it. Perhaps as a reaction to this, those publishing DSM-III-R and preparing DSM-IV have shown signs of a more evangelistic approach to the promulgation of and use of the U.S. classification.

The first seven sections of this volume deal with the various clinical syndromes; each is introduced by a subeditor and finishes with an overview. These sections vary considerably in their length and detail, but those on affective disorders and schizophrenia are particularly useful. The discussion of the background of the classification of affective disorders leans heavily on the NIMH Collaborative Study on the Psychobiology of Depression and is more interesting because of this. The chapter on schizophrenia and schizophreniform disorders is particularly clearly written and contains a variety of constructive criticisms. There is, however, an all too brief attempt to summarize problems of broad and narrow definitions of schizophrenia and the vices and virtues of first-rank symptoms in making a diagnosis of schizophrenia. More space and more accurate references are required to do justice to this familiar problem.

The chapter dealing with anxiety and panic is disappointingly brief, although this is no doubt an opinion with the advantage of hindsight in view of controversies about the importance that should be given to panic disorder as a disorder in its own right. (One of the few major differences between DSM-III and DSM-III-R is in the precedence given to panic disorder over agoraphobia in DSM-III-R.)

There is a particularly useful review of borderline personality disorder, and the studies reviewed provide a good example of how a concept can be defined so as to be reliable between observers but yet still not be proven to have any particular clinical validity. It is all too easy nowadays for diagnosticians and classifiers to become preoccupied with measurements of reliability, since they are so much simpler than measurements of validity. Reliability represents agreement between two measures of the same trait or diagnostic concept, obtained through maximally similar methods (e.g., parallel forms of the same test or different observers using the same test). Validity represents agreement between two measures of the same trait or diagnostic concept obtained through maximally different methods. With respect to borderline personality disorder, there seems to be growing agreement that there is something there to be tested, but for the moment it would be wise to agree with the author of this particular chapter that borderline personality can only be regarded as a "vagabond and transitory boundary label" which nevertheless merits further investigation.

The final sections deal with broader issues such as exclusion criteria, hierarchical effects, and a variety of suggestions for the revision of DSM-III. There are also sections on the multiaxial approach and comments on the clinical, educational, and administrative applications of DSM-III. Some of the suggestions

and criticisms in these sections have been accommodated by *DSM-III-R*, but most of the discussion is still relevant to those preparing *DSM-IV* and other classifications.

An overall theme that runs through most of the sections of this book is that the U.S. classifications must be based on the latest reliable and systematic clinical evidence. The importance of this cannot be denied, but this volume also illustrates some of the dangers of an overenthusiastic adherence to the desire to be modern and up-to-date. Research done in different centers and at different times often produces conflicting results, and fashions of both ideas and techniques are likely to change. Those in charge of the construction of new classifications or the revision of existing ones probably need to be somewhat on the conservative side in reviewing recent work and new evidence. The best compromise and balance between new findings and clinical customs is not easily found.

JOHN E. COOPER, M.D.
Nottingham, England

The Joint Commission Guide to Quality Assurance, by the Joint Commission on Accreditation of Healthcare Organizations. Chicago, JCAHO, 1988, 148 pp., \$55.00.

Those involved in hospital administration are especially alert to the workings of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Respect and alliance admixed with fear, anger, and resistance can often be found in the relationship between the clinical and managerial staff of a hospital and the JCAHO. As a clinical administrator, when I saw notice of this *Guide* I thought that I had better take a look at it. At best, it might be helpful in the now obligatory quality assurance activities of every health care organization. At worst, I would at least know what dreaded fate awaits me.

I was reassured to examine *The Joint Commission Guide to Quality Assurance*. The authors of this monograph aim to be understood. The book design uses a brief text with outlines of the material in the margins, frequent tables and figures, and numerous examples that clarify and illustrate how to do what has been described. Chapters are well organized and summarized. Basic points are emphasized, occasionally to excess. The language, by and large, is colloquial and understandable.

Several important topics and chapters stand out. Quality assurance is broken down into three components: clinical services, medical staff, and organization-wide quality assurance. Chapters are devoted to each of these areas. Monitoring of clinical services includes review of special care units (psychiatric units, for example), ambulatory services, social work, and substance abuse services. Monitoring of medical staff includes review of the quality of clinical care provided by the professional staff, the quality of medical records, and the appropriateness, safety, and effectiveness of medication. Organization-wide quality assurance includes utilization review, infection control, and risk management.

Indicators of care are defined and categorized as structure, process, and outcome. Structure refers to whether the organization has the staffing and procedures for good care; process refers to whether patients receive a good standard of care; outcome refers to whether patients have a positive outcome from the care delivered. A 10-step process for quality assurance is repetitively presented. These 10 steps walk the novice through the basics of quality assurance: assigning

responsibility, identifying the scope of the review, establishing indicators and thresholds for evaluation, taking action, and reporting.

The reader can obtain an overview of quality assurance, informed by a brief history of the past workings of the old Joint Commission on the Accreditation of Hospitals (before it was the JCAHO) and can see the general direction in which the field is moving. For example, future JCAHO reviews of psychiatric services may encompass the efficacy and safety of prescribed medications. The reader will understand both the goals of such a review and how to prepare for it from a good reading of this book.

The *Guide* is not specific for psychiatry. All medical specialties are encompassed in the monograph, as are all health care organizations. This lack of specialization is both a limitation and a contribution for clinicians working in a psychiatric facility. We might appreciate more specific material for our field, but the lack of specialization informs us of the expectations of our medical and administrative colleagues and demonstrates the general principles that are applied. The *Guide* tends to be repetitious: subjects and procedures are described multiple times throughout. Despite these criticisms and the rather steep price, *The Joint Commission Guide to Quality Assurance* is an accomplishment and a valuable document. Of course, this is a highly technical work. However, it is well done and will serve as an important resource to clinical departments, clinical administrators, and quality assurance officers and staff.

LLOYD I. SEDERER, M.D.
Cambridge, Mass.

The Chief Resident as Manager, by Neal Whitman, M.P.A., Ed.D., Elaine Weiss, Ed.D., and Lawrence Lutz, M.S.P.H., M.D. Salt Lake City, Department of Family and Preventive Medicine, University of Utah School of Medicine, 1988, 143 pp., \$16.00 (spiral-bound paper).

For many, chief residency is a trial by fire. When the fire gets intense, some how-to literature would be a help. In the little that is written on how to be a chief resident, the emphasis has been on the highly variable nature of this job, the lack of training for it, and the ambiguity of job descriptions, when job descriptions exist at all (1). Even though about 70% of the chief resident's time is spent in administration, virtually no training in administration is provided (2).

Attempting to remedy this dearth of information, the authors of *The Chief Resident as Manager* have drawn a useful parallel between the work of a chief resident and that of a mid-level manager and describe in explicit detail what they see as the specific managerial functions of a chief resident. The strength of their work is that while elaborating this managerial and task-oriented approach, they still address sufficiently the all-important and complex interpersonal aspects of the chief residency. The chief resident, they explain, acts like a foreman in a factory who is responsible to higher levels of authority and yet is still one of the workers. The authors offer specific management strategies for the chief resident who is learning this complex role, so that the book is actually a compendium of management strategies adapted for the chief resident. Chapters such as "Developing Your Game Plan," "Managing Time," and "Resolving Conflict" begin with case examples and then develop relevant managerial concepts and interpersonal strategies.

For example, in "Delegating Work," the authors describe

an inefficient chief resident who brings home an excessive amount of work. He finds that the work interferes with his personal time and feels overwhelmed by his responsibilities. According to Whitman, Weiss, and Lutz, the solution for this resident is to use definite techniques for getting others to help with the workload. They describe six steps for effective delegation: 1) Describe the framework of the assigned task. 2) Describe the desired results. 3) Identify available resources. 4) Ask for commitment. 5) Ask for initial ideas. 6) Agree to a timetable and an evaluation plan. A self-evaluation questionnaire at the end of this chapter challenges readers to assess their abilities to delegate.

Interpersonal skills are vital to the chief resident. In "Developing Your Game Plan" the authors advise assessment of personal style in dealing with people:

In working with others, it is important to understand some things about yourself. What are your strengths and weaknesses? What situations bring out the best in you? How well do you communicate with others? In order to answer some of these questions, we believe it is important for you to look at how you communicate with others. It is also important for you to consider how other people communicate with you.

"Giving Feedback" is an instructive chapter on building team cohesion and encouraging competence. The authors advocate an interactive process aimed at educating workers and reinforcing their adaptive skills.

The book refers to most of the last decade's literature on the chief residency and incorporates the authors' own experiences working in seminars for chief residents. For instance, in "Developing Your Game Plan," the authors cite survey data from nearly 1,500 residency programs indicating that the top three priorities of chief residents are building teamwork, delegating duties, and giving feedback. They have used these concepts in developing a 2-day course for chief residents as managers at the University of Utah School of Medicine and continually highlight them throughout the text.

Unfortunately, missing from the book is a discussion of the ways in which staff dynamic processes affect the work of the chief resident and how they can be modified by the chief resident. Green (3), writing mostly about psychiatric chief residents, described the chief resident as a transference figure:

[The chief resident is] a necessarily ill-defined figure whose ambiguity is the product of conscious and unconscious projections and distortions on the part of members of the residency training program. This description implies a widespread wish among staff members to transform the chief resident into a powerful transference figure so that he may fill this need within the therapeutic milieu.

Role expectations can drive the success or failure of a chief resident and are important concepts that complement the work developed in *The Chief Resident as Manager*.

Perhaps the greatest strength of this book is that both the managerial techniques and interpersonal skills discussed here are applicable to chief residents in any specialty. Senior residents who read this book before taking on the job of chief resident will probably feel better prepared for their work. This book tells you how to get the job done and how to use your own style to do it. It will prove a useful guide for those chief residents who enter the job with little preparation, high

expectations, and great responsibilities. For psychiatric chief residents, it will be important to supplement this book with literature on staff dynamic issues. It would also be well for staff to read this book in order to understand and, at least, not work against what the chief resident is doing.

REFERENCES

1. Grant I, Dorus W, McGlashan T, et al: The chief resident in psychiatry. *Arch Gen Psychiatry* 1974; 30:503-507
2. Ruiz P: Psychiatry: when nobody wants to be chief resident. *Resident and Staff Physician*, March 1977, pp 57-61
3. Green SA: The chief resident as reluctant staff therapist. *Am J Psychiatry* 1975; 132:1078-1081

RONALD J. KOSHES, M.D.
Washington, D.C.

Consent and the Incompetent Patient: Ethics, Law, and Medicine, edited by Steven R. Hirsch and John Harris. London, Gaskell (Washington, D.C., American Psychiatric Press, distributor), 1988, 96 pp., £7.50 (paper).

This book transcribes a meeting of the Royal Society of Medicine held in December 1985 concerning patient consent to treatment and research. The participants were responding to a document entitled *Consent to Treatment*, which was issued by the British Mental Health Commission in 1985. *Consent and the Incompetent Patient* includes presentations by a member of the British Mental Health Commission as well as by professionals with expertise in the areas of law, ethics, medicine, psychiatry, and geriatrics. Transcriptions of the discussions following the presentations are also included in the book.

What makes this book interesting may very well stem from the point of departure in 1776 between British and U.S. law. British law derives its foundation from its common law heritage. U.S. law has not only retained the British common law foundation but has adopted a rights-based model through the Bill of Rights and subsequent Constitutional amendments. The common law crime of committing battery upon a patient who cannot give a competent consent is the core issue of this conference. Another interesting point is that do-not-resuscitate orders, durable power of attorney, and living wills as used in the United States are essentially nonexistent in Britain due to the operational effects of the British medical-legal system. Despite the operational differences between the British and U.S. systems, physicians in both settings face conflicts between the ethical dictum to treat those who are in need and the legal rights that interfere with this treatment in those who are incapable of providing consent. Although the conundrum posed by this conflict has been problematic for U.S. physicians for a considerable time now, this difficulty has become an area of increasing ethical concern for our British counterparts.

The multiauthor structure of this book creates an unevenness in readability. Although the clinical-ethical problems highlighted will strike a resonant chord in most readers, *Consent and the Incompetent Patient* will likely appeal only to a highly selected readership—those interested in comparative law and ethics in medicine. Therefore, unless one is deeply interested in the nuances of evolving British law, this

book best remains on the shelves of a library because it will not significantly add to one's general understanding of medical ethics.

GREGORY B. LEONG, M.D.
Los Angeles, Calif.

Ethics and Psychiatry: Toward Professional Definition, by Allen R. Dyer, M.D., Ph.D. Washington, D.C., American Psychiatric Press, 1988, 168 pp., \$32.00.

In this important book, psychiatrist-philosopher Allen Dyer attempts a fundamental reexamination of what passes for ethics in our specialty. He has surveyed the field and found it wanting. Dyer contends that in narrowly pursuing an ideal of objectivity and universality in moral analysis, contemporary bioethics has divorced ethical action from its human context. Thus, he states, bioethics often has a "paradoxically dehumanizing effect on medical practice" and has attempted to establish itself as "a rival rather than a coordinate [clinical] discipline" (p. 5). Against this dominant trend, Dyer advocates the application of Michael Polanyi's "post-critical" philosophy. For Polanyi, the ideal of objective, completely specifiable knowledge is not only unattainable but positively misleading. Instead, he speaks of the unavoidably subjective component of all knowledge, that all we know is known personally and not simply abstractly or objectively.

Because of this novel philosophical perspective, psychiatrists will find that Dyer's book reads more like a clinician's guide than a philosopher's treatise. The author is less concerned with careful logical analysis than with human understanding. Accordingly, there is no list of principles of medical ethics here from which one deduces ethical conduct. Instead, the book engages the long list of ethical issues facing psychiatry from a different perspective. The relatedness and interdependence of persons are stressed more than their autonomy. Virtues are emphasized more than principles. Rather than replacing the Hippocratic Oath as an outmoded relic, we are advised to continue to learn from its wisdom. Altruism and idealism are proposed as concepts fundamental to a comprehensive moral vocabulary. The values of public service and personal care are advocated as foundational to psychiatry's status as a profession.

The philosophically sophisticated reader will find this book more evocative than definitive. The author's analysis, although highly suggestive, is unsystematic. As a result, those schooled in contemporary bioethics will find it frustrating. It is not tightly reasoned and provides few specific answers. Particularly disappointing is Dyer's failure to incorporate the seminal work of Alasdair MacIntyre (1), whose elegant critiques of modern moral philosophy would have provided an excellent resource for this project.

For practicing psychiatrists who daily live with the ambiguity and complexity of clinical work with patients, this book will provide wise counsel. It is refreshing to spend time with this book, whose author obviously possesses a clinician's mind and, even more, a clinician's heart. *Ethics and Psychiatry* deserves wide readership in our profession. It provides needed balance to the hegemony of the abstract, rationalist school in contemporary bioethics.

REFERENCE

1. MacIntyre A: After Virtue. Notre Dame, Ind, University of Notre Dame Press, 1981

ROGER C. SIDER, M.D.
Grand Rapids, Mich.

SCHIZOPHRENIA

Schizophrenia and Aging: Schizophrenia, Paranoia, and Schizophreniform Disorders in Later Life, edited by Nancy E. Miller and Gene D. Cohen. New York, Guilford Press, 1987, 367 pp., \$40.00.

Mr. Y was admitted to Saint Elizabeths Hospital in 1928 while serving in the Navy. His hospitalization was precipitated by an evaluation at sick call for sluggishness that revealed marked unresponsiveness and verbalization of odd comments. He was given a diagnosis of dementia praecox. The following represents his mental status examination on admission.

Appearance and behavior. Moves slowly into the room and sits as far from the examiner as he can. Looks at floor or ceiling and has an unconcerned, inadequate manner. Only speaks in answer to a question.

Emotional response. Dull, washed-out facial expression; very flattened affect.

Verbalization. Stream of talk is meager, retarded, yet at times relevant and coherent; his answers are given slowly and in a low-toned voice only after he ponders each question.

Thought content. Retardation of thought; has no suicidal ideation; voices no complaints; says no one has it in for him; no hallucinations are elicited.

Sensorium and cognition. Not interested in environment; oriented to date, place, and person; memory sporadically incorrect for both recent and remote events; correctly answers questions like naming largest river in this country, who is President; adds, subtracts, and multiplies accurately; says he is not sick but "I don't know" if Saint Elizabeths is the correct place for him.

In 1988, 60 years later, Mr. Y was 80 years old and had been a patient at Saint Elizabeths Hospital continually since 1928. His mental status examination at that time was as follows.

Appearance and behavior. Neatly self-dressed, enters examination room and sits away from the examiner. Stares at the floor, never making eye contact with the examiner. Speaks only in answer to a question. Clinicians report that he has no relations with other patients, and he initiates conversation with only one member of the staff, Mrs. A. Day is spent on the grounds observing cars about which he is quite informed. The only behavior that causes considerable concern is his very skilled picking of locks.

Emotional response. Flattened expression can be broken at times with considerable anger.

Verbalization. Most answers are one to three barely audible words after some delay. When angry, he is loud and will emit a barrage of modern-day profanities.

Thought content. Nothing elicited. Behavior does not suggest hallucinations.

Sensorium and cognition. Oriented to date, place, and person. Aware of staff and patient changes on the ward and will ask Mrs. A what has happened to a person no longer on the ward. Can handle simple mathematical tasks. Doesn't believe that he is mentally ill, but does want to remain at Saint Elizabeths.

For a person with schizophrenia, how typical has the aging process been in the case of Mr. Y? *Schizophrenia and Aging* brings together what is known anatomically, physiologically, biochemically, pathologically, and psychopathologically about the course of these patients as well as clarifying what new studies are needed.

Even while granting that patients with schizophrenia constitute a heterogeneous population with a very broad range of outcomes, we can state some generalities that hold. The chapter by Winokur et al. in this book discusses the Iowa 500 study, which found that first-rank signs (bizarre behavior, depressed mood, and grandiose delusions) decrease with age, whereas avolitional and cognitive deficits get significantly worse. In other words, there is a decrease in positive signs and an increase in negative signs. Positive signs are made worse by overstimulation, whereas negative signs are made worse by an impoverished social environment. Other studies found the cognitive deficits of schizophrenia over time to be independent of age, years of hospitalization, amount of ECT received, or amount of medications received. Separate chapters by Lamb and Harding report that decreased pressures in patients' later years are often associated with stabilization and a functioning at their highest level. A number of studies have shown that these patients have a significantly higher mortality rate than "normal" persons but that they may be less prone to cancer.

In addition to presenting studies describing the typical person with schizophrenia, Miller and Cohen include in this book papers on late-onset schizophrenia, an entity that emerged in U.S. psychiatry with *DSM-III-R*. The comprehensive *Schizophrenia and Aging* ends with four chapters on the treatment of the elderly patient with schizophrenia.

Since some symptoms of the aging process may be difficult to distinguish from schizophrenic symptoms, this book's summary of findings and suggested directions for research are important and germane to those wanting an understanding of schizophrenia.

ROGER PEELE, M.D.
Washington, D.C.

Delusional Beliefs, edited by Thomas R. Oltmanns and Brendan A. Maher. New York, John Wiley & Sons, 1988, 352 pp., \$37.95.

Psychiatrists talk about delusions but do not necessarily think about delusions. This book offers theories as to how the mind produces delusions. The editors' strategy is to examine the symptom teased away from the various diagnoses in which it appears.

The *American Psychiatric Glossary* (1) defines delusion in two short sentences, and the psychiatrist on the go might boil it down to three words: unshared false beliefs. Oltmanns and Maher raise the caution of what they call the "Martha Mitchell effect." That unfortunate woman's belief that the White House was darkened by illegal activity and that her husband was collaborating with it was dismissed as delusional—until the Watergate scandal was exposed.

Oltmanns and Maher find many definitions of delusion (including those in *DSM-III*) to be wanting. With their contributors, they offer thoughtful and complicated alternatives. The editors downplay their own ideas so as not to shift the spotlight from their contributors. When it is all over, there are no firm answers but, instead, a call for further data and scholarly inquiry.

The editors review the literature on delusion and find four principal theories of causation that have attracted followers. One belief is that a personality trait is the culprit, such as Freud's theory that paranoia is generated by unconscious homosexual desires. Another theory implicates faulty thinking or information processing. A third implicates poor social skills with resultant isolation and lack of social feedback. The fourth, ascribed to by Maher, sees delusions as logical explanations for anomalous subjective experience.

This book's strength lies in its presentation of interesting and provocative theoretical arguments. For example, Maher states that the thought processes which keep an individual with chronic schizophrenia glued to a pet delusion are fully comparable to the thinking of a scientist who repeatedly ignores new data contradicting a pet scientific theory. Maher believes that neither the schizophrenic patient nor the scientist has more disordered thoughts than the other; instead, both are attempting to make sense of their unique experiences.

I found some of the book's ideas to bypass the complexity of the real world. For example, as an argument for the idea that delusions may be culture bound, Oltmanns cites the fact that in the Soviet Union, dissidents are hospitalized for "reformist delusions" which we in the United States would not consider delusions at all. My suspicion, however, is that the majority of psychiatrists in the U.S.S.R. disagree with these diagnostic shams but are too frightened to voice their opinions.

Most of the contributors to this book are academic psychologists, reflected in part by their being more interested in nonpsychoanalytic aspects of theoretical psychopathology than are psychiatrists (at least in the United States). One chapter by psychiatrists, which deals with treatment, parts from the editors' philosophy of studying the delusion apart from the diagnosis. This chapter describes varying treatments for varying diagnoses, and rightly so. Even though the book was published in 1988, this chapter has no citations past 1985 and is mysteriously obsessed with pimozide.

The book is not easy for either the casual reader or the clinician looking for a quick overview in a 10-minute break between patients. There is a lack of tight editing and an anemic subject index. The chapters average 20 pages, and only some have the helpful summaries that most journals insist on for their articles.

The book does not answer many of the questions it poses; some may find this a disappointment, others an inspiration to further inquiry. Those with an interest in theoretical psychopathology who are already familiar with or interested in the current literature on delusions should have the greatest interest in this book. It would be a worthy addition to a reading list in a doctoral level course in psychopathology.

REFERENCE

1. Stone EM (ed): *American Psychiatric Glossary*, 6th ed. Washington, DC, American Psychiatric Press, 1988

JOHN HOCHMAN, M.D.
Tarzana, Calif.

Clinical Research in Schizophrenia: A Multidimensional Approach, edited by Roy R. Grinker, Sr., and Martin Harrow. Springfield, Ill., Charles C Thomas, 1987, 418 pp., \$60.50.

This is a seminal work by a group of outstanding clinical researchers and scholars of schizophrenia. It represents a

model and standard for thoughtful research into some of the cardinal psychopathological and cognitive features of schizophrenia, its course, prognosis, and outcome. It also represents the rich harvest from a large, multidisciplinary, longitudinal research program, the Chicago Follow-Up Study, conducted under the leadership of Grinker and Harrow, and includes an excellent review of this study at the University of Chicago. Although its specific focus is the study of schizophrenia from several different vantage points (broad and narrow concepts of schizophrenia and short- and long-term outcomes), it has as a broader goal to integrate diverse theories and approaches to the human mind and abnormal psychocognitive functioning as represented by schizophrenic abnormalities. In working toward this goal, the book successfully transcends at times the boundaries of schizophrenia and presents behavioral data on a number of other psychotic and nonpsychotic disorders.

The book is well organized and articulated in a conceptually clear fashion, reflecting the overall research plan and coherence of the research program. Part one presents the theoretical underpinnings and methods of the research. Every student of schizophrenia is confronted with the task of integrating in some coherent way the many behavioral, psychological, cognitive, and biological deficits found in this complex group of disorders. Grinker proposes in a convincing fashion the use of a general systems theory approach to accommodate all the findings. His research approach to the manifestations and mechanisms of schizophrenic dysfunctions is highly specific and simultaneously complex. Although the etiological theories regarding the underlying biological factors in schizophrenia are relatively unspecific, Grinker's investigation of the behavioral, psychological, and cognitive deficits in schizophrenia shows a high degree of details and appreciation of the complexity of the underlying mechanisms. However, the wish to create order out of this multitude of findings by postulating one single underlying predominant dysfunctional mechanism does not do justice to the disparity of cognitive, perceptual, and integrative dysfunctions in schizophrenia.

Part two covers diagnosis and the Chicago Follow-Up Study and some cardinal psychopathological manifestations. It contains M. Silverstein's classic challenge of the pathognomonic status of Schneider's first-rank symptoms for schizophrenia. Also included is P. Holzman's early studies of abnormal-pursuit eye movements with their genetic implications. M. Harrow's study of anhedonia, a negative symptom, across several diagnostic categories not only provides another example of careful phenomenological study but also opens the hypothesis for a continuum concept for some of the so-called schizophrenic symptoms across diagnostic boundaries. In further studies of the relationship between anhedonia and other psychopathological characteristics, Harrow's group found a significant relationship with depression. Our own group found a similar relationship of the negative syndrome with depression in young patients with acute schizophrenia (1).

Part three presents careful and interesting studies on disordered cognition in schizophrenia. Longitudinal studies of schizophrenic thought disorder show a biphasic course. Severe positive thought disorder during the acute phase is not associated with poor outcome, but it is linked to later poor outcome when present in the postacute phase. Furthermore, the presence of positive symptoms such as positive thought disorder, delusions, and/or hallucinations after the acute phase of hospitalization seems to separate out a more severely disordered subgroup of schizophrenic patients with poorer outcome.

Overall, a number of studies show the presence of more severe overall level of thought disorder, including bizarre idiosyncratic thinking, in schizophrenic patients than in patients with other psychoses. Schizophrenic patients with a high degree of thought disorder also seem to be unable to appreciate the social appropriateness of their own verbalizations, which points to an impaired self-perspective in these patients.

Part four includes studies on prognosis, course, and outcome. In carefully conducted prospective longitudinal studies, a majority (55%) of the schizophrenic patients studied showed a negative outcome, with either poor functioning in most areas or an episodic course with deterioration. Only 21% showed continuously good outcome or an episodic course with improvement. These results are not dissimilar from those of other major outcome studies (2, 3). Schizoaffective patients show outcomes that are intermediate between those of schizophrenic patients and patients with affective disorder. Predictors for good outcome include acute onset, good previous work history, advanced education, higher IQ, and older age. Most of these predictors relate in one way or another to cognitive intactness, which may be one of the underlying pathogenic factors influencing the course of schizophrenia.

One of the book's important strengths is its focus on the study of young patients with nonchronic schizophrenia in the early stages of their illness together with careful longitudinal follow-up investigation. Another strength is its detailed use of phenomenological investigations, although the newer attempt to classify positive versus negative symptoms is only partially reflected in the studies reported. The phenomenological strength of these studies constitutes their limitation as well. Ultimately, phenomenology needs to be tied to underlying biological mechanisms or biological markers in order to yield hypotheses and explanations regarding pathogenesis and etiology. Few researchers in schizophrenia have been able to make that connection in a valid and reliable fashion. To criticize these authors for this limitation, therefore, is perhaps premature. In all, this book belongs on the shelf of every serious student of schizophrenia.

REFERENCES

1. Kay SR, Lindenmayer J-P: Outcome predictors in acute schizophrenia: prospective significance of background and clinical dimension. *J Nerv Ment Dis* 1987; 175:152-160
2. Ciompi L: Catamnestic long-term study on the course of life and aging of schizophrenics. *Schizophr Bull* 1980; 6:606-632
3. Huber A, Gross A, Schuttler R, et al: Longitudinal studies of schizophrenic patients. *Schizophr Bull* 1980; 6:592-605

JEAN-PIERRE LINDENMAYER, M.D.
New York, N.Y.

PSYCHOANALYSIS

Freud's Theory of Psychoanalysis, by Ole Andkjaer Olsen and Simo K  ppe; translated by Jean-Christian Delay and Carl Petersen. New York, New York University Press, 1988, 447 pp., \$42.00.

This book, written by two research associates in the Psychological Laboratory of the University of Copenhagen, is in my opinion mistitled. It should read *Our New Idiosyncratic Rereading of Freud's Psychoanalysis, Modeled After Lacan's*

Return to Freud. The authors begin with a lengthy first section in which they present a theory containing a vast number of sociological and historical generalizations that may or may not be true. The following statements are examples. "It seems necessary to suppose that when psychoanalysis arises as a 'new' theory of the subject, it does so because society has in fact given rise to a 'new' subject" (p. 5). "We assume that the influence of this educational philosophy led to the appearance of a new psychological personality structure" (pp. 10, 11). "There is also evident correlation between the evolution of the sphere of production and the mechanistic subject concept" (p. 17). "Most psychoanalysts are politically conservative" (p. xxi). "The monotonous nature of the housewife's tasks, the intensified care of children, the necessity of being at close quarters all day, the absence of the father from the home, all contributed to establish what could be called a frictional sexuality between these subjects [housewives and children]. In short, the sphere of intimacy generated increasing amounts of nervousness and irritability, not to mention the binding of heightened emotional and imaginative activity" (p. xvii). This last quotation also gives the flavor of the translation.

The issue at hand is not whether these generalizations, which sound like popular sociology or popular psychology and which fill the first part of the book, are correct but that no evidence is given for innumerable contentions of this nature. We are asked to accept the authors' orientation and their declarations. I am not qualified to judge sociological treatises, but I suspect that many experts in that field would not agree with the sweeping delineations of eras and trends in sociology and political history offered by the authors. Furthermore, I think Freud would not agree with their basic contention that sociological conditions produced new subjects; this is certainly a long way from his primarily intrapsychic theory of drives, conflicts, and defenses and the resultant compromise formations, which he considered to be universal and historically similar in the human psyche regardless of the economic, political, and sociological circumstances. Indeed, in "Civilization and Its Discontents" (1), Freud was specifically skeptical of Marxist political theory, which purported to produce a new human subject by changing the means of production, and referred to aggression as an "indestructible feature of human nature" (p. 114).

The reason this issue is so important is that the entire rereading of Freud by the authors, in the spirit of Lacan's "return to Freud," is based on their stated attempt to replace or supplement Freud's phylogenetic explanations in many areas with "sociogenetic" explanations—explanations based on the social history of the subject through the past centuries rather than its biological history (p. xvii). The authors do not convince the reader that the speculations and generalizations on which their social history of the subject is based are any more valid than Freud's biological (or pseudobiological) and phylogenetic speculations and assumptions. They also do not demonstrate that their rereading of Freud would be any more acceptable to Freud himself than would that of Lacan. They admit that their book is not for beginners, and that is why I fret that it is mistitled; it really belongs in a course on Freud and philosophy. I doubt that it would be helpful or interesting to the average practicing psychiatrist who turned to it for clinical understanding or for an elucidation of Freud's practice of psychoanalysis. Indeed, the authors tell us, again without supporting argument, that "if we focus our attention on psychoanalysis as a therapeutic method of treatment for neurotic afflictions, then we find that its results are not particularly uplifting" (p. xxi).

The four remaining sections of the book, which are much longer than the first, describe Freud's published work and even his life from the authors' sociogenetic standpoint. On the whole, their review seems adequate enough, although of course in such a long book there are bound to be statements that a reader would disagree with. For example, we are told that Stekel's work "contains the seeds of a theory of the death wish, anticipating an aspect of Freud's theory of the death drive" (p. 137), a contention that, in my opinion, confuses the concept of a death wish with Freud's entirely different concept of a death instinct. In general, the authors give Stekel far more credit for originality than he deserves. As another example, in their discussion of the phallic phase of development and the Oedipus complex there is a curious lack of emphasis on the sexual or libidinal thrust of that situation and a repeated tendency to describe the sadistic, power-seeking, or "mastery of the mother" (p. 295) aspects. Along with a number of references to domination and control in the phallic phase (pp. 273, 391, 392), we are given the authors' own rather different theory of sexuality (p. 367), which is not clearly differentiated from that of Freud. Indeed, in the last 100 pages of the book, on the genesis and the structure of the subject, to use the authors' terms, it seems that they are using Freud's work as a springboard to describe their own theories.

The authors describe the famous case histories of Freud thinly, concentrating mainly on the dynamics involved and, consistent with their lack of concern with psychoanalysis as a treatment, presenting little on the many important issues of clinical practice that have filled the literature on Freud's case histories and are of current interest to the practicing psychiatrist and psychoanalyst. Their review invites comparison with Gay's biography of Freud (2) and with many other books on Freud, including my own (3), in which the human interaction and clinical practical issues are placed in the foreground of Freud's psychoanalysis.

Here and there some of the authors' comments on Freud's work are questionable or misleading. For example, they seem to miss the crucial point of Freud's early work on aphasia in their discussion of the subject (p. 328), which was not only his concept of separate systems of word presentations and thing presentations but also his idea that in pathology the normal connection between word presentations and thing presentations is severed. Freud carried over this crucially important notion from his organic studies on aphasia to his subsequent metapsychological conceptualizations of neuroses and psychoses. The authors' discussion of the death instinct (p. 355) confirms their confusion of death wishes with Freud's metaphysical concept of a death instinct. The discussion of female sexuality misses Freud's chronic ambiguity and ambivalence on the subject, again inviting comparison with Gay's biography (2), and it adds what I found to be a puzzling comment that both the boy and the girl think that the penis is more sexually sensitive than the girl's organ (p. 391).

The overall problem with this book, which clearly represents a strenuous and sincere effort, is that it covers too many areas of highly controversial theory in too many disciplines and blurs the distinction between Freud's admittedly more naive nineteenth-century orientation to science and current postmodern philosophy and science. It also does not clearly distinguish between Freud's repeated definitive statements that his psychoanalysis was a natural science and many contemporary readings of Freud, with which I am sure he would have been in great disagreement. This makes it unsatisfactory for those who wish a clear exposition of Freud's theory of psychoanalysis and very hard going for the reader who is

unfamiliar with current trends in Continental philosophy and current controversies about the return to Freud. By trying to cover sociology, history, general psychiatry, philosophy, and psychoanalysis all at once, the authors render themselves vulnerable to confusion and misunderstanding and are prone to oscillate between superficial or thin presentations and highly technical discussions, which tend to jolt the reader back and forth. Also, in such a voluminous coverage there are inevitable superficial judgments, such as their statement that Leibniz is "known primarily for his theory of monads" (p. 29), which a philosopher would consider quite misleading. Examples are their definition of Leibniz's monads as "infinitesimal particles" (p. 29), which a philosopher would state is simply wrong, and their claim that Nietzsche and Schopenhauer did not influence Freud (p. 24), which a historian or philosopher carefully reading Freud's work or studying his life would consider incorrect. Therefore, I cannot recommend this book to psychiatrist readers.

REFERENCES

1. Freud S: Civilization and its discontents (1930[1929]), in Complete Psychological Works, standard ed, vol 21. London, Hogarth Press, 1961
2. Gay P: Freud: A Life for Our Time. New York, WW Norton, 1988
3. Chessick R: Freud Teaches Psychotherapy. Indianapolis, Hackett, 1980

RICHARD D. CHESSICK, M.D., PH.D.
Evanston, Ill.

Freud: Appraisals and Reappraisals, vol. 2, edited by Paul E. Stepansky. Hillsdale, N.J., Analytic Press, 1988, 200 pp., \$29.95.

Freud: Appraisals and Reappraisals, vol. 3, edited by Paul E. Stepansky. Hillsdale, N.J., Analytic Press, 1988, 201 pp., \$29.95.

The appraisals and reappraisals in these books are of Freud himself more than his theory, biography more than clinical technique. When most successful, they enlarge our understanding of Freud's character and motivations and the effect of these on his output. Volume 1 (1) contained often fresh and exciting essays that reflected Freud in new and interesting ways; the best of the new papers in volumes 2 and 3 continue that tradition. None of the authors under review is a psychiatrist, and at times one may feel removed from psychological issues, adrift in dry academic theses. Each volume contains three papers. One book succeeds but the other fails in bringing Freud and his work to life.

Volume 2 begins ominously. Peter Homans's lengthy, wordy, poorly written, weakly reasoned essay seeks to analyze Freud with an awkward mix of self psychology and sociological theory. In "Disappointment and the Ability to Mourn: De-Idealization as a Psychological Theme in Freud's Life, Thought, and Social Circumstance, 1904-1914," Homans reformulates a period of Freud's life as a series of mergers with and de-idealizations of self-objects: Adler, Jung, Michelangelo and Moses, various essays and ideas, Rome, Judaism, etc. Attempting to follow Kohut (2), Homans uses de-idealization and other self psychological concepts mechanically and universally. He scarcely adds to the established understanding that Freud's involvements

were often intense and ambivalent. Such use of jargon deforms more than it informs. Homans indulges in the common excesses of psychohistorical extrapolation with insufficient apology and with scant result. Editor Paul Stepansky, who opens the book with a valiant vanguard defense of this piece, would perhaps have done better to edit it more firmly. I regret to report (but it is irresistible) that the reader quickly de-idealizes this tiresome essay.

By contrast, Richard Geha writes in a spare, lucid style. His "Freud as Fictionalist" is the bright note of this volume. Neatly reviewing the Freud-as-artist literature, Geha argues persuasively that Freud was a cryptonovelist, even providing evidence that Freud himself, despite his emphasis on a scientific stance, acknowledged this in later life. Midway through the essay, however, Geha shifts his energies to demonstrating, after Nietzsche, Vaihinger, and others, that all of human experience is subjective and hence fictive. This familiar epistemological stance undercuts his earlier exposition of Freud's particular genius as a writer. The shift from biographical specifics to philosophical generalities may disappoint readers interested in Freud's creative literary approach to his case material.

Patricia Herzog's brief "The Myth of Freud as Anti-Philosopher" bears a lackluster resemblance to Geha's paper. Like Geha, she uses the case history of the Wolf Man and other texts to unmask Freud the scientist, this time as philosopher *manqué*. This is hardly news: Freud's ambitious genius encompassed clinical, scientific, artistic, humanistic, and philosophical interests. Emphasizing his scientific role was a political necessity, crucial to Freud and to followers like Ernest Jones to win clinical acceptance of psychoanalytic treatment. It is as naive to take literally Freud's insistence that he was simply a scientist as to assume that Jones's biography is unbiased. By arguing with Freud and Jones against his selectively scientific posture, Herzog perpetuates a specious dichotomy between artists and humanists. Clearly Freud was both, transcending categories. Herzog catalogs Freud's unflattering references to philosophy, then abandons the position that he was an antiphilosopher to remark that "Freud's attitude toward philosophy was subtle and complex" (p. 182). Would that her argument were so. On balance, volume 2 is a disappointment.

Volume 3, however, shimmers with intellectual light. John Kerr's "Beyond the Pleasure Principle and Back Again: Freud, Jung, and Sabina Spielrein" is a novel, skillful argument by analogy and allusion. Kerr explores Freud's development of the still puzzling death instinct as a response to theories advanced some 8 years earlier by his rival Jung in *Transformations and Symbols of the Libido* (1911-1912) by using Spielrein's "Destruction as a Cause of Coming Into Being" (1912). Kerr's explanation is unprovable but convincing. Even those skeptical of his conclusions will find this elegant essay worthwhile for connecting these texts and particularly for illustrating the interpersonal forces that shaped all three works by the authors in this psychoanalytic triangle.

A difference that speaks volumes: whereas Herzog's paper simply listed Freud's antiphilosophical citations, Kerr also shows Freud attacking philosophy but interprets this as a reprisal against Jung's theoretical and spiritual aspirations, insightfully demonstrating the importance of metapsychological infighting on Freud's theorizing. The exploration of Freud's motivations and personal stake in his theory adds another dimension to reading Freud's work.

I anticipated the return (from volume 1) of the irrepressible Peter Swales with pleasure. His scrutiny of Freud's early case material is gradually redefining the origins of psycho-

analysis. "Freud, Katharina, and the First 'Wild Analysis'" is a tour de force, a genuine reappraisal of Freud's clinical data based on painstaking research. As he did in volume 1, Swales brilliantly reconstructs an early "analysis," at once supporting and undermining the original case history. He reveals the identity of Katharina in *Studies on Hysteria* (3), recreating her history of present illness and contributing family history, outcome data, and photographs to boot.

Swales shows the importance of suggestion, intentional and otherwise, in Freud's early treatment and the master's selective, tendentious approach to data to justify his a priori assumption of sexual etiology. Swales does not hesitate to play analyst to the Analyst, making provocative yet often convincing interpretations. The bad boy of Freud scholarship ends one of his many long footnotes with the parenthetical, "Am I not the only true Freudian?" (p. 154). He is chock-full of fascinating speculations, anecdotes, asides, unfinished projects, trivia, and other delicious tidbits. Although not a clinician, he is a gifted writer with good psychological instincts. His naughtily playful prose continues to gleam, yet he is less manic, less voluble, and less distractible than he has been. His paper is an achievement.

Robert Holt's concise "Freud's Adolescent Reading: Some Possible Effects on His Work" concludes volume 3 with thoughtful book reviews of three "notorious" (p. 168) best-sellers that Freud and his friends informally studied as teenagers. These are intriguing anticipations of Freud germinating in the mid-nineteenth century. Holt makes a good case for the influence of Buechner's scientific materialism and Feuerbach's and Strauss's renegade theologies on Freud's general outlook, specific theories, and prose style. Holt succeeds in suggesting the experience Freud might have had reading these texts, thereby enhancing our understanding of his creative process. Volume 3 of *Freud: Appraisals and Reappraisals* is a find for those interested in the forces that helped to shape Freud and his writing.

REFERENCES

1. Stepansky PE (ed): *Freud: Appraisals and Reappraisals, Contributions to Freud Studies*, vol 1. Hillsdale, NJ, Analytic Press, 1986
2. Kohut H: Creativity, charisma, group psychology: reflections on the self-analysis of Freud, in *The Search for the Self: Selected Writings of Heinz Kohut*, vol 2. Edited by Orenstein PH. New York, International Universities Press, 1976
3. Breuer J, Freud S: *Studies on Hysteria* (1895[1893-1895]): *Complete Psychological Works*, standard ed, vol 2. London, Hogarth Press, 1955

JOHN C. MARKOWITZ, M.D.
New York, N.Y.

A Fresh Look at Psychoanalysis: The View From Self-Psychology, by Arnold Goldberg. Hillsdale, N.J., Analytic Press, 1988, 275 pp., \$29.95.

This book is a collection of 18 published and unpublished essays written over a number of years by Arnold Goldberg. The volume is divided into four parts: Theory, Empathy, Character, and Clinical Papers. All of the essays reflect the author's deep regard for his profession, his efforts to internalize knowledge of many persuasions that bear on psychoanalytic concerns, and his intellectual involvement with psychoanalytic self psychology. In the preface, Goldberg sets the

tone by expressing his astonishment at two opposing camps of self psychology: the true believers and the determined unbelievers. He maintains that the "easiest roads to follow are those of total dismissal or full-fledged allegiance; the most difficult is the struggle to find an appropriate place to fit new ideas." On the basis of my reading, it is clear that Goldberg has chosen the most difficult path.

As I read this book, I was reminded of Kohut's concern before he died that his work was being spoiled by a number of overenthusiastic, cliquish, arrogant self-appointed disciples who promoted his theories without grasping their meaning (1). In sharp contrast, Arnold Goldberg would seem to be the kind of interpreter that Kohut—or anyone else—would want to have: someone who clarifies and expands sometimes fragily constructed ideas so that their merits might be assessed. I was also reminded of a theme that runs through Winnicott's recently published letters (2). Winnicott insisted that ideas be expressed and discussed; they should not be put forth aggressively or in propagandist ways and "then defended in a way that can be called paranoid." When ideas are presented in the latter style, they become unacceptable or are labeled dissentient no matter how legitimate and how valuable their contribution. Like Winnicott, Goldberg insists that true believers and determined nonbelievers lack the intellectual maturity needed to advance the discipline. Intellectually mature advocates of new theories consider thoughtfully and systematically the psychoanalytic literature as a whole as well as relevant literature from other fields (scientific philosophy, semantics, linguistics, and hermeneutics). If this literature is not considered, it is impossible to establish how a new theory complements, differs from, and extends what is already in place and, by extension, it is impossible to assess a new theory's merits.

In parts one and two of this book, Goldberg explores the nature of science and the relationship between empathy and theory. Parts three and four, by comparison, speak more directly to the specifics of self psychology. Obviously, I cannot do justice to all 18 essays in the space of this review; therefore, I will limit my remaining comments to Goldberg's ideas about the nature of science and about empathy. His writings on these matters awaken in the reader a professional responsibility at least to become familiar with self psychology.

Goldberg maintains that those who claim total allegiance to a theory are simply unaware of how science progresses. The scientific method requires that all research be open to reexamination and revision in the light of new evidence. Continued reexamination and revision mean that research is both a process and a dialogue. It is a process because conclusions are never considered final; it is a dialogue because it is a critical conversation among the minds of the past, present thinkers, and a multitude of professionals. Reexamination and revision should be equated not with personal animosity or abandonment of established theory but with efforts to reduce gaps in understanding. The fact that all knowledge is unfinished compels us to participate in the revision process because efforts to resist new ideas stifle scientific progress. The broader implication is that the psychoanalytic community cannot be defined by a theory because, if the theory is shaken, the community is shaken as well. Furthermore, strict adherence to a particular theory does not permit growth. The unifying thread must be training and a common sense of purpose. A healthy and vibrant community must contain mechanisms by which its beliefs and theory can be revitalized. If I am not mistaken, Goldberg offers empathy as the mechanism for revitalization. Empathy is "first and foremost a method of observation." It is a data-gathering tool:

"The data of one's mind are just as available as the data of the physical world Gathering up all the cues given by one person to another, plus the information told to us by the other person, allows a shared meaning to be formed" (p. 99).

Empathy needs to be guided by theory because observers, uninformed by theory, do not know what to look for. To explain the place of theory, Goldberg uses the analogy of students looking into a microscope for the first time. Students usually see nothing until they are given a theory and set of logical steps to follow. Theory, however, does not determine the conclusions reached. To reach a conclusion on the basis of theory alone is bad science; rather, the data are accumulated to verify the theory. It is important to wait until all the evidence is in. Otherwise we cannot be open to the possibility of discovery that arises when a gap exists between observation and guiding theories. "The misuse of theory will lead to premature closure without enough data and the supposed accumulation of data without theory leads to the lack of selective capacity."

The revitalization mechanism is triggered when efforts are made to close the gap between observation and theory. The

efforts may take the form of considering previously neglected theory or establishing a new theory to frame the observations.

Personally, I find comfort in Goldberg's writings. They call for everyone involved in psychoanalytically oriented work to become part of the revitalization process. Goldberg's principles also help us to discount the idea that empathy is all that is needed to "cure": "Empathic people without analytic theory are not analysts, just as theoreticians without empathy cannot practice." In my opinion this is a book that needs to be reread periodically because it is pleasing and stimulating in its complexity.

REFERENCES

1. Gedo JE: *Conceptual Issues in Psychoanalysis: Essays in History and Method*. Hillsdale, NJ, Analytic Press, 1986
2. Rodman FR (ed): *The Spontaneous Gesture: Selected Letters of DW Winnicott*. Cambridge, Harvard University Press, 1987

JOAN FERRANTE, PH.D.
Highland Heights, Ky.

Reprints of Book Forum reviews are not available.

Letters to the Editor

Cardiac Problems in ECT

SIR: ECT is a safe and effective treatment for major depression (1). The emergence of cardiac problems accounts for most of the morbidity, even in individuals considered at low risk (2, 3). We present a case of ventricular tachycardia and idioventricular dysrhythmia in a man with no history of cardiac problems who underwent ECT for recurrent major depression.

Mr. A, a 71-year-old white man in excellent physical health, had been treated on two previous occasions with ECT without complication. His only known health problem was benign prostatic hypertrophy, for which he had undergone a transurethral resection 5 years before the current hospital admission. He was taking no medications. Results of a physical examination, ECG, and laboratory studies were unremarkable. ECT was undertaken.

Before the first ECT, the patient received 0.3 mg of glycopyrrolate, 100 mg of methohexital, 70 mg of succinylcholine, and 100% oxygen. His blood pressure was 150/84 mm Hg. Continuous cardiac monitoring demonstrated normal wave form and a heart rate of 84 bpm. Following application of the current, frequent premature ventricular contractions (PVCs), including triplets, were noted on the heart monitor. Mr. A's heart rate rose to 160 bpm and his blood pressure to 200/140 mm Hg. Ventricular tachycardia at more than 200 bpm ensued, with blood pressure of 240/170 mm Hg. Administration of 100 mg of lidocaine produced a wide-QRS complex bradycardia. The further administration of 0.4 mg of atropine resulted in a normal sinus rhythm with a rate of 96 bpm. Blood pressure normalized over the following hour. Seizure duration was 40 seconds.

The following changes were made in medication before the second ECT. Because of the patient's anxiety, 100 mg of fentanyl were added, and glycopyrrolate was concomitantly reduced to 0.1 mg. As prophylaxis against the reemergence of ventricular ectopy, 100 mg of lidocaine were administered. Current was left the same, pending evidence that the presence of lidocaine necessitated a change. Succinylcholine, methohexital, and oxygen were given as before. Following the application of current, a supraventricular rate of 160 bpm again resulted, with the recurrence of PVCs, including triplets. Mr. A's blood pressure rose to 220/150 mm Hg. His heart rate spontaneously decreased to 30–56 bpm, with a wide-QRS complex pattern, interpreted by a cardiologist as idioventricular in origin. Seizure duration was 85 seconds. Continued ventricular bradycardia responded to 0.2 mg of atropine, with conversion to a normal sinus rhythm. At the patient's request, ECT was discontinued.

Twenty-four-hour Holter monitoring obtained 72 hours after ECT demonstrated the occurrence of rare, asymptomatic singlet PVCs and atrial premature contractions. Twelve-lead ECG 7 days later showed no ectopy. Now

taking a tricyclic antidepressant, the patient is functioning at his premorbid level without apparent depression or cardiac symptoms.

Admittedly, life-threatening complications are rare with ECT. We present this case as a reminder, however, that such complications can occur, even in individuals considered at low risk (3). It is desirable, therefore, that those who administer ECT be skilled at resuscitative measures and be knowledgeable about medications used to counter cardiac dysrhythmias. We also note that while others (4) have found that lidocaine prevented adequate seizure activity during ECT, this was not true with our patient.

REFERENCES

1. Heshe J, Roeder E: Electroconvulsive therapy in Denmark. *Br J Psychiatry* 1976; 128:241–245
2. McKenna G, Engle RP, Brooks H, et al: Cardiac arrhythmias during electroshock therapy: significance, prevention, and treatment. *Am J Psychiatry* 1970; 127:530–533
3. Gerring JP, Shields HM: The identification and management of patients with a high risk for cardiac arrhythmias during modified ECT. *J Clin Psychiatry* 1982; 43:140–143
4. Hood D, Mecca S: Failure to initiate electroconvulsive seizures in a patient pretreated with lidocaine. *Anesthesiology* 1983; 58:379–381

SYLVIA DENNISON, M.D.
RICHARD N. FRENCH, M.D.
Indianapolis, Ind.

Adverse Psychiatric Reaction to Ketoconazole

SIR: Adverse effects on the CNS are among the most frequently reported drug reactions (1, 2), and 3% of all patients receiving drug therapy may be expected to develop significant psychological disturbances (3). We report a case of an adverse psychiatric reaction to ketoconazole, a reaction which to our knowledge has not been previously described.

Mr. A, a 51-year-old man, was admitted to the hospital for investigation of dysuria and suspected malignant cells in his urine (no malignancy was found eventually). His past medical history was unremarkable except for urethritis, most probably gonococcal, 20 years earlier. During the routine admission interview, the patient mentioned that he had had an adverse psychiatric reaction to ketoconazole, and a psychiatric consultation was requested.

The patient had no psychiatric history and had never experienced any psychopathological symptoms except in association with ketoconazole. He had no history of alcoholism or drug abuse. On interview he was found to be an extrovert with exhibitionistic and hysteriform personality traits. He described himself as what would be considered a

chronic, mild hypomanic character, with no episodes of depression or suicidal ideas.

Mr. A had first used ketoconazole (for urethritis) with no adverse reaction. During the next several years he self-administered five to six 4-day courses of ketoconazole, 400 mg b.i.d., for urethritis. Each time, 1–2 hours after ingesting the drug, he heard an inner voice commanding, "Kill yourself," and experienced the same command as a visual image on an imagined screen. These persistent commands were repeated continuously for about an hour and were felt to be so senseless and repellent that he actively resisted them. He felt impelled to drink large amounts of water, the idea being to dilute the drug and lessen its impact.

The whole phenomenon would disappear completely after about an hour. The patient established the connection between ketoconazole and this reaction but continued to self-administer the drug for urethritis because he feared complications.

Ketoconazole, an imidazole derivative, is a broad-spectrum antifungal agent, available as oral and topical preparations. Pharmacological studies claim that CSF penetration by ketoconazole is minimal, but clinical observation of side effects such as headaches, dizziness, somnolence, and photophobia suggests probable CSF involvement (4). Other imidazole derivatives (clotrimazole, miconazole) and the antifungal griseofulvin have been reported to cause psychiatric symptoms (5), but to the best of our knowledge such reactions to ketoconazole have not been previously described.

The fundamental problem in an individual drug reaction is to establish a clear cause-effect relationship between the drug and its adverse effect. This case fulfills the criteria for a definite relationship, namely: 1) a reasonable temporal sequence after administration of the drug, 2) disappearance of symptoms upon stopping the drug (dechallenge), and 3) reappearance of symptoms upon repeating the exposure (rechallenge). The patient had no psychiatric symptoms except in association with ketoconazole, and the quality of his symptoms was clearly ego-alien. Hence, we conclude that this case represents a genuine, if idiosyncratic, reaction to ketoconazole.

REFERENCES

1. Martys CR: Adverse reactions to drugs in general practice. *Br Med J* 1979; 2:1194–1197
2. Davison K: Drug-induced psychiatric disorders. *Med International* 1983; 36:16–19
3. Kaplan HI, Freedman AM, Sadock BJ: *Comprehensive Textbook of Psychiatry*, 3rd ed, vol 2. Baltimore, Williams & Wilkins, 1980, pp 1437–1451
4. Gilman AG, Goodman LS, Rall TW, et al: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 7th ed. New York, Macmillan, 1985, pp 1226–1228
5. Martindale W (ed): *The Extra Pharmacopoeia*, 28th ed. London, Pharmaceutical Press, 1982, pp 714–726

R.Z. FISCH, M.D.
A. LAHAD, M.D.
Jerusalem, Israel

Panic Disorder Following 2-Chloroprocaine

SIR: We have read with interest reports of panic disorder following administration of procaine in patients who had no prior history of psychiatric disturbance (1, 2). Your readers

should be aware that an acute panic reaction is possible in patients receiving the local anesthetic 2-chloroprocaine for epidural analgesia. This situation is most common in young parturient women requiring obstetric surgery. We report a recent case at our institution.

Ms. A, a 25-year-old woman, delivered a live male baby with epidural analgesia. She received 8 ml of 0.25% bupivacaine and 10 ml of 1% lidocaine during labor without complications. Sixteen hours postpartum, she was taken to the operating room for tubal ligation. She received 20 ml of epidural 3% 2-chloroprocaine in 3-ml incremental doses until a bilateral T4 sensory level was obtained. Within 3 minutes of receiving the total local anesthetic, the patient reported that the "operating room ceiling was falling" and that she was "going to die." She became confused and agitated and was subsequently given a general anesthetic, from which she emerged without sequelae. This patient had no history of psychiatric problems before this admission.

We have had three additional panic reactions under similar circumstances in the past 12 months when we used epidural 2-chloroprocaine for patients requiring elective Caesarean section. We have not seen this reaction with either lidocaine or bupivacaine after inadvertent intravascular injection. Saravay et al. (3) reported anxiety and confusion in patients who received low doses of lidocaine administered intravenously. We have noted obtundation following either lidocaine or bupivacaine when these were inadvertently administered intravenously.

Silber and D'Angelo (2) have suggested that elevated cerebral tissue concentrations of free procaine may be the cause of Hoigne's syndrome. However, one cannot rule out cerebral tissue concentrations of the metabolites of procaine or chloroprocaine as another cause of this syndrome. A common metabolite of both drugs is diethylaminoethanol. We agree with Silber and D'Angelo's hypothesis. We also believe that cerebral tissue concentrations of chloroprocaine and/or its metabolites may have been responsible for the "doom" anxiety that we saw in our patients. Chloroprocaine is similar in structure to procaine, with the exception that a chlorine atom is substituted for hydrogen at the 2 position of the aromatic ring. Minimal amounts of the drug are metabolized in neural tissue (4). After neural blockade, termination of a block when procaine or chloroprocaine is being used depends on outward diffusion of the drug. We have not noticed these symptoms after accidental intravascular injection of chloroprocaine. This may be because its plasma hydrolysis rate is higher than that of procaine, allowing less of the drug to ultimately penetrate cerebral tissue.

It is important for anesthesiologists and psychiatrists to be able to distinguish panic attacks from hypersensitivity reactions to local anesthetics because the management of these conditions differs. It may, furthermore, be prudent for psychiatrists to recommend to anesthesiologists that they avoid chloroprocaine or procaine for any patient with a history of emotional disturbance.

REFERENCES

1. Biddle N, McCormack H: Panic disorder and the procaine penicillin G (letter). *Am J Psychiatry* 1988; 145:1317
2. Silber T, D'Angelo L: Doom anxiety and Hoigne's syndrome (letter). *Am J Psychiatry* 1987; 144:1365

3. Saravay SM, Marke J, Steinberg MD, et al: "Doom anxiety" and delirium in lidocaine toxicity. *Am J Psychiatry* 1987; 144: 159-163
4. Foldes FF, Aven MH: Hydrolysis of procaine and 2-chloroprocaine in spinal fluid. *J Pharmacol Exp Ther* 1952; 105:259-264

WILLIAM E. ACKERMAN, M.D.
JAMES C. PHERO, D.M.D.
MUSHTAQUE M. JUNEJA, M.D.
Cincinnati, Ohio

Use of Imaging Techniques for Schizophrenic Patients

SIR: Bruce Cohen, M.D., and colleagues (1) recently described the MRI and CT scan results in a heterogeneous group of psychotic patients, highlighting the superiority of MRI over CT in visualizing brain structure but finding little clinical relevance to the subtle differences detected. They raised familiar issues relating to suitable control groups, effective drug treatment, and length of illness. As these findings are of great interest to the study of schizophrenia, we would like to report our own early observations with these imaging techniques in medication-free, first-episode schizophrenic patients.

As part of an ongoing prospective study of first-episode schizophrenia being conducted at the University of Western Ontario (2), five untreated male schizophrenic patients (ages 18-28 years), whose illness was defined by clinical examination and the Present State Examination (3), and five age- and sex-matched control subjects were examined by MRI (GE Signa 1.5-tesla scanner). All of the patients had previously had CT scans that were judged to be normal. The MRI scans were examined blindly by three neuroradiologists who evaluated the scans with particular attention to cerebral atrophy, ventricular size, white matter changes, and structural lesions. Previous high interobserver reliability in visual inspection of these parameters in CT scans has been reported by this group (4). There was complete agreement in the group in eight cases. In seven of these cases (four schizophrenic patients and three control subjects), the results were entirely normal. One schizophrenic patient had moderate generalized atrophy and a hyperintense lesion in the left parietal white matter with no known clinical significance. There were two cases in which there was disagreement on the presence or absence of mild atrophy, but these were both control patients.

Although detailed analyses were not completed, no major differences were noted between the schizophrenic patients and the control subjects on most parameters. Although one schizophrenic patient had a white matter change, it was not clinically significant. White matter hyperintensities on MRI are seen in a variety of conditions, and these findings, in general, are now the subject of controversy (5). MRI appears sensitive to structural change, but given the findings in the control subjects, the measurement and interpretation of subtle neuroradiological changes must be viewed cautiously. It appears likely that the MRI technique will be used in attempts to replicate many of the early CT studies, although its greatest potential may be in the area of structural measurement of previously poorly visualized areas, e.g., the temporal lobes or corpus callosum, or in utilizing the unique physiochemical dimensions of MRI, such as relaxation times (6). Despite this, it still seems unlikely that gross structural pathology will be the most clinically relevant variable in the schizophrenic picture.

REFERENCES

1. Cohen BM, Buonanno F, Keck PE Jr, et al: Comparison of MRI and CT scans in a group of psychiatric patients. *Am J Psychiatry* 1988; 145:1084-1088
2. Waring EM, Lefcoe D, Carver C, et al: The course and outcome of early schizophrenia. *Psychiatr J Univ Ottawa* (in press)
3. Wing JK, Cooper JE, Sartorius N: *The Measurement and Classification of Psychiatric Symptoms: An Instructional Manual for the PSE and CATEGO Programs*. New York, Cambridge University Press, 1974
4. Lee D, Fox A, Vinuela F, et al: Interobserver variation in computed tomography of the brain. *Arch Neurol* 1987; 44:30-31
5. Kertesz A, Black SE, Tokar G, et al: Periventricular and subcortical hyperintensities on magnetic resonance imaging. *Arch Neurol* 1988; 45:404-408
6. Conlon P, Trimble MR: Magnetic resonance imaging in psychiatry. *Can J Psychiatry* 1987; 32:702-712

PATRICK CONLON, M.D.
DAVID PELZ, M.D.
EDWARD WARING, M.D.
DANIEL LEFCOE, M.D.
RAHUL MANCHANDA, M.D.
London, Ont., Canada

Prodromal Symptoms

SIR: The article "Duration and Symptoms of Bipolar Prodromes" by George Molnar, M.D., and his colleagues (1) drew attention to an important and still largely overlooked phenomenon. The possibility of preventing relapse and minimizing maintenance medication by paying attention to early warning symptoms (harbingers) was pointed out in a paper I presented at the VI World Congress of Psychiatry in Honolulu in 1977; in a further study (2) I defined their clinical characteristics.

The term "harbinger" was originally chosen for these prodromal symptoms because it seemed to be peculiarly apt. Its derivation from the Old French *hebergere*—a provider of lodging—is more explicit. A harbinger was not only a forerunner of an approaching army in medieval times; his job was to assess the adequacy of food and shelter for the oncoming soldiers in the territory they were intending to occupy. If we liken a relapse in an illness to an oncoming army of enemy soldiers, the aptness of the metaphor becomes more apparent. Harbingers are quantitatively and qualitatively different from the oncoming army (the illness), and we may, by starting or changing the treatment program, prevent the harbingers from finding the "food and shelter" needed for the "occupation" of the patient by the illness.

Although there may be some semantic and other differences between the prodromal symptoms described by Dr. Molnar and associates and the harbingers I previously described, I strongly endorse the authors' final sentence in their article: "If such patients and their family members are educated to recognize the patient's characteristic prodromal symptoms, recurrences of affective disorder could be treated earlier and perhaps more effectively."

The question remains: How are we going to educate our colleagues to recognize this phenomenon to the benefit of their patients?

REFERENCES

1. Molnar G, Feeney MG, Fava GA: Duration and symptoms of bipolar prodromes. *Am J Psychiatry* 1988; 145:1576-1578

2. Roper PDL: Harbingers of relapse in psychiatric illness. *Annals of the Royal College of Physicians and Surgeons of Canada* 1983; 16:44-49

P.D.L. ROPER, M.D.
Montreal, Que., Canada

A Lycanthropic Murderer

SIR: Among the innumerable metamorphoses of humans into animals, the magical transformation into a wolf constitutes one of the most ancient and universal beliefs. Lycanthropy is characterized by a delusion of physical transformation in which the patient believes he or she has been changed into a wolf. To our knowledge, modern literature has produced only three true cases (1, 2); two other observations concern transformation into a dog (3, 4). We should like to describe a 28-year-old man who was imprisoned for physical violence leading to the death of a man he had invited to his home.

Mr. A's mother died when he was 18 months old. The father, who was unable to look after his children, sent him to live with his uncle, with whom he lived for 11 years. He went to school until the age of 14 and was then placed by a judge in several hostels. He did not work, he drank, and his companions were delinquents. He constantly invented unbelievable stories and often changed his living quarters. He was sentenced several times for theft, assuming false identity, assault and battery, and illegal carrying of firearms.

Mr. A declares that he has been a werewolf for a long time and that this accounts for his behavior. "It's when I was bitten by a rabid dog . . . When I'm emotionally upset, I feel as if I am turning into something else; my fingers go numb, as if I had pins and needles right in the middle of my hand; I can no longer control myself . . . I get the feeling I'm becoming a wolf. I look at myself in the mirror and I witness my transformation. It's no longer my face; it changes completely. I stare, my pupils dilate, and I feel as if hairs are growing all over my body, as if my teeth are getting longer . . . I feel as if my skin is no longer mine."

Mr. A's female companion confirms his convictions and pathological behavior: "[In] the night he wasn't quite asleep . . . and was smacking his head against the walls, and . . . he was like a beast, a wolf . . . I even had to put up with funny things from the sexual point of view, like a beast!"

Mr. A is a physically sturdy man of average height. Results of an EEG, cerebral scanning, and a neurological examination were normal. He has no loss of memory, no hallucinations or delusions of reference, no catatonic behavior. His behavior is overly dramatic and theatrical. According to the WAIS, he has an IQ of 81. A Rorschach test shows that he has a borderline personality. His MMPI profile shows spikes for paranoia and schizophrenia. His DSM-III-R diagnoses on axis I are depersonalization disorder (300.60) and alcohol dependence (303.90) and on axis II, antisocial personality disorder (301.70) and borderline personality disorder (301.83); on axis III, he has a history of convulsions in infancy. On axis IV and V, his code is 5.

The interpretation of lycanthropy has moved from a superstitious religious model to a medical model (hallucinatory delusions involving animals and hysterical psychosis). Lycan-

thropy is, at present, seen as a depersonalization disorder. So far, according to our observations, it is closer to hysteria and mythomania (5) in an antisocial personality.

REFERENCES

1. Surawicz F, Banta R: Lycanthropy revisited. *Can Psychiatr Assoc J* 1975; 20:537-542
2. Rosenstock HA, Vincent KR: A case of lycanthropy. *Am J Psychiatry* 1977; 134:1147-1149
3. Coll PG, O'Sullivan G, Browne PJ: Lycanthropy lives on. *Br J Psychiatry* 1985; 147:201-202
4. Jackson PM: Another case of lycanthropy (letter). *Am J Psychiatry* 1978; 135:134-135
5. Dupré E: La mythomanie: étude psychologique et médico-légale du mensonge et de la fabulation morbides. *Le Bulletin Médical* 1905; number 23, pp 263-268; number 25, pp 285-290; number 27, pp 311-315

MICHEL BENEZECH, M.D.
JACQUES DE WITTE, M.D.
JEAN JACQUES ETCHEPARRE, M.D.
MARC BOURGEOIS, M.D.
Bordeaux, France

Psychological Factors in Preterm Childbirth

SIR: The conclusion reached by Haim Omer, Ph.D., and George S. Everly, Jr., Ph.D. (1) that preterm labor can be understood to be a result of excessive psychophysiological arousal was well supported by the data they presented.

However, the authors did not address one unexplained paradox: the inhibitory effect of sympathomimetic agents on premature labor despite their otherwise stimulatory effect (2). Although Drs. Omer and Everly reported that epinephrine inhibits uterine contractions, the widespread clinical use of β -adrenergic agents such as terbutaline and ritodrine in premature labor was not mentioned. Anxiety is "commonly observed" with the use of terbutaline (*Physicians' Desk Reference*) and intravenous ritodrine (3). Oral ritodrine causes anxiety in 5%-10% of patients, and a further 10%-50% report somatic symptoms of anxiety, including tremor, palpitations, headache, and nausea. A model that notes the tocolytic effects of relaxation and reduced mental stress must also account for the simultaneous reduction of uterine contractility and the frequent induction of anxiety caused by these agents.

REFERENCES

1. Omer H, Everly GS Jr: Psychological factors in preterm labor: critical review and theoretical synthesis. *Am J Psychiatry* 1988; 145:1507-1513
2. Gillman AG, Goodman LS, Rall TW, et al (eds): Goodman and Gilman's *The Pharmacological Basis of Therapeutics* (7th ed). New York, Macmillan, 1985
3. Pernoll ML, Benson RC (eds): *Current Obstetric and Gynecologic Diagnosis and Treatment*. Norwalk, Conn, Appleton & Lange, 1987

VALERIE D. RASKIN, M.D.
Chicago, Ill.

SIR: I read with interest the review by Drs. Omer and Everly of the role of psychological factors in preterm birth. This is an intriguing and potentially important area of research. In particular, the authors are to be commended for

bringing to the attention of American readers the interesting work being done in the Federal Republic of Germany regarding the relationship of a lowered rheobase to preterm birth. I do feel, however, that the authors' major assertion—that psychological stress and psychopathology are a cause of preterm birth—is a reasonable hypothesis that, unfortunately, has not yet been proved (1).

Drs. Omer and Everly pointed out numerous methodological shortcomings in the studies they reviewed, and with these concerns I can only concur. However, even the investigations that they feel offer support for their notions cannot be accepted unequivocally. For example, consider one study which the authors seemed to accept with few reservations—the Omer et al. investigation of the relationship of anxiety and SCL-90 scores to preterm birth (2). Neither the quality of prenatal care nor the nutritional status of the mother was assessed in this study—factors which logically could be either a cause or an effect of concurrently assessed psychological distress. In addition, these authors reported the curious and unexplained use of a Mann-Whitney U test in all comparisons of group means. With interval data of the sort provided by the SCL-90 or the Spielberger Anxiety Inventory, use of this test is generally inappropriate. Inspection of the group standard deviations reported in the paper seems to show that if a parametric test such as the t test had been used, all comparisons would have been nonsignificant.

A second problem with the review by Drs. Omer and Everly is their exclusive focus on preterm birth as an outcome measure. The usual technique of establishing gestational age—questioning the mother about her last normal menstrual period—can be quite unreliable and may result in categorizing up to 25% of term births as preterm (3). Since none of the studies the authors cited mentioned confirming fetal age by ultrasound examination, it can probably be assumed that the much less accurate technique of questioning about the last normal menstrual period was used.

A third concern is the central role the authors assigned to chronic stress in the provocation of preterm birth. To my knowledge, it has never been shown that the relatively enduring changes in patterns of neuroendocrine secretion which characterize physiologic stress are associated with the naturally occurring stressors they discussed. It might be just as reasonable to hypothesize that habituation to such stimuli occurs in pregnant women, rather than "accumulation" as the authors suggested. Indeed, a laboratory study has suggested that pregnancy may be a period characterized by reduced responsiveness to stressors (4).

I believe that it is indeed possible that psychological factors contribute to preterm birth. Inadequate nutrition and drug use may be a consequence of psychopathology or exposure to stressors, effects which are no less real and no less important than psychophysiologic sequelae. The authors' model may prove to be heuristic; I do feel, however, that it has limited explanatory value because there is at present little evidence that there is a phenomenon to explain.

REFERENCES

1. Istvan J: Stress, anxiety, and birth outcomes: a critical review of the evidence. *Psychol Bull* 1986; 100:331-348
2. Omer H, Elizur Y, Barnea T, et al: Psychological variables and premature labour: a possible solution for some methodological problems. *J Psychosom Res* 1986; 30:559-565
3. Kramer MS, McLean FH, Boyd ME, et al: The validity of gestational age estimation by menstrual dating in term, preterm, and postterm gestations. *JAMA* 1988; 260:3306-3308

4. Nisell H, Hjemdahl P, Linde B, et al: Sympathoadrenal and cardiovascular reactivity in pregnancy-induced hypertension. *Am J Obstet Gynecol* 1985; 152:554-560

JOSEPH A. ISTVAN, M.D.
Portland, Ore.

The Psychiatric Chief Residency

SIR: We are encouraged by the article of Michael A. Silver, M.D., and Luis R. Marcos, M.D. (1) regarding the perceived need to strengthen and formalize training for psychiatrist-executives. It was mentioned that the psychiatric chief residency is frequently the "initial experience in administration." As psychiatric chief residents at the Medical College of Virginia, we would like to give further emphasis to this notion and suggest that the chief residency provides crucial role modeling for residents in psychiatry.

The psychiatric chief resident is in a unique position to learn and master many skills as a beginning administrator. Looney et al. (2) identified the model of the "interface chief." We believe that the model of the interface chief creates an optimal setting for the chief to learn administrative process. As elaborated by Colenda (3), this model allows the chief resident to move independently across multiple boundary interfaces and thus fosters a broader conceptualization of the chief resident's role in terms of the structural and functional relationships within the department and hospital. In this way junior residents, along with the faculty, are able to observe the administrative behavior of, or modeling by, the chief resident, which leads to a heightened institutional expectation of the administrative role.

The "identity" of the chief resident must be established at the beginning if he or she is to be an effective role model. A strong identity facilitates clarity regarding the crucial issues of boundaries, power, and authority. Early opportunities to participate in workshops (e.g., the Albert Einstein Annual Chief Resident's Conference), specific administrative supervision by an experienced faculty person, and directed readings about the management process are necessary tools that help reinforce this identity. Also, the interface chief will avoid systemic stumbling blocks if he or she is chosen by a selection process that includes both resident and faculty input rather than selection based solely on a chairman's or residency training director's discretion.

To help distinguish the special administrative role of the chief resident, the position should be openly discussed and promoted. Incentives such as increased salary, along with sponsored conferences and workshops, should be offered. Because of the chief resident's close relationship with the chairman and residency director, he or she should be involved in helping to design administratively oriented didactic seminars for residents.

More than ever, graduating psychiatric residents are confronted with choosing from a diverse range of practice settings. Unfortunately, residents often leave residency unskilled in integrating clinical expertise or understanding of human behavior with the exigencies imposed upon clinicians by "managed" health care systems, public or private.

The health care environment is in critical need of talented psychiatrist-executives (1) who can administrate from a perspective of understanding clinical issues as well as systems. In our opinion, a philosophical commitment to this issue should begin earlier in training. Therefore, we advocate upgrading the administrative role of the psychiatric chief resident in

preparation for the realities and challenges of today's complex psychiatric practice environment.

REFERENCES

1. Silver MA, Marcos LR: The making of the psychiatrist-executive. *Am J Psychiatry* 1989; 146:29-34
2. Looney JG, Engelberg SJ, Gode RO, et al: The psychiatric chief residency: a preliminary training experience in administrative process. *Am J Psychiatry* 1975; 132:729-733
3. Colenda C: The psychiatry chief resident as information manager. *J Med Educ* 1986; 61:666-673

CLAUDIA BEMIS, M.D.
RANDALL FEHR, M.D.
Richmond, Va.

Imipramine for Patients With Alzheimer's Disease With and Without Depression

SIR: The article "Double-Blind Trial of Imipramine in Alzheimer's Disease Patients With and Without Depression" by Burton V. Reifler, M.D., M.P.H., and associates (1) was instructive in underscoring the observation that Alzheimer's disease can yield, in some of its manifestations, to treatment. For management purposes, Alzheimer's disease should not be considered with therapeutic nihilism as an entity for which there is no known cure, but rather as a syndrome that poses a variety of cognitive, affective, and behavioral challenges. To these, psychiatry is especially well placed to respond (2).

I would like to suggest that another conclusion may be drawn from this study. Dr. Reifler and associates stated, "We do not see this as a negative study because imipramine was not superior to placebo but as a positive study because the patients improved regardless of treatment condition." The improvement in question was deemed to have resulted from the supportive attention given to the subjects. Thus, it seems admissible to conclude that this approach represents a form of psychotherapy which may be a valuable therapeutic modality for elderly patients with moderate degrees of depression, both those with Alzheimer's disease and perhaps even those without Alzheimer's disease. A wider recognition of the value of supportive attention should lead to a diminution in the polypharmacy to which the elderly are especially prone (3). Other benefits of a reduction in pharmacotherapy would include the obviation of the well-known adverse effects of antidepressants. Further research to delineate the characteristic features of this form of psychotherapy and of the patients who are responsive to it is now needed.

REFERENCES

1. Reifler BV, Teri L, Raskind M, et al: Double-blind trial of imipramine in Alzheimer's disease patients with and without depression. *Am J Psychiatry* 1989; 146:45-49
2. American Psychiatric Association Task Force on Alzheimer's Disease: The Alzheimer's disease imperative: the challenge for psychiatry (editorial). *Am J Psychiatry* 1988; 145:1550-1551
3. Lamy PP: Prescribing for the Elderly. Littleton, Mass, PSG, 1980

J. PIERRE LOEBEL, M.D.
Seattle, Wash.

SIR: In their article on the use of imipramine in Alzheimer's disease patients, Dr. Reifler and associates drew firmly positive conclusions about the efficacy of antidepressants in Alzheimer's disease. If one were to read just the abstract, one might infer that "both groups" which improved were the only two groups mentioned in the preceding sentence, i.e., a depressed and a euthymic one. Thus, the conclusion that depression is a treatable condition in Alzheimer's disease seems to suggest a response to imipramine.

In fact, the study revealed that depressed Alzheimer's disease patients improved as much when taking placebo as when taking imipramine and that imipramine caused exacerbation of dementia in both the depressed and the nondepressed groups (as measured on the Dementia Rating Scale). Thus, rather than cautioning physicians to use "the lowest clinically effective dose" of imipramine for depressed Alzheimer's disease patients, the authors might have proposed rejection of the use of this agent in this disease. It may be that less anticholinergic antidepressants would prove to be safe and more effective than imipramine; this certainly should be addressed in the future.

The fact that depressed subjects did improve when taking placebo is explained by the supportive nature of weekly clinic visits. It would be interesting to know which variable on the Hamilton Rating Scale for Depression improved and what aspects of the weekly visits may have been therapeutic. It is encouraging to see concrete evidence of improvement in Alzheimer's disease; it is vital that we begin to understand the factors involved.

MICHAEL SERBY, M.D.
New York, N.Y.

SIR: Dr. Reifler and associates reported that the depression of all their patients improved comparably with either imipramine or placebo. At the completion of the study, the depressed patients treated with imipramine had a total drug plasma level of 119 ng/ml (72 ng/ml of imipramine plus 47 ng/ml of desipramine). Citing one reference (1), the authors stated that this blood plasma level is within the generally accepted therapeutic range. In a more recent report (2), the APA Task Force on the Use of Laboratory Tests in Psychiatry reviewed imipramine levels and clinical outcome and found that the percentage of patients responding favorably increases as combined blood levels of imipramine and desipramine are increased up to 200-250 ng/ml.

For a valid comparison of a drug treatment and placebo the drug must be given at an adequate dosage, which ideally should be based on blood levels. This study did not answer the question of whether imipramine or supportive therapy is the treatment of choice in moderately depressed Alzheimer's patients, as the imipramine-treated group appears to have had an inadequate trial.

REFERENCES

1. Hollister LE: Tricyclic antidepressants. *N Engl J Med* 1978; 299:1106-1109
2. Task Force on the Use of Laboratory Tests in Psychiatry: Tricyclic antidepressants—blood level measurements and clinical outcome: an APA task force report. *Am J Psychiatry* 1985; 142:155-162

RAYFORD W. THWEATT, M.D.
Birmingham, Ala.

Dr. Reifler Replies

SIR: The central question in these three thoughtful and well-reasoned letters is, To what, exactly, did these patients respond? I believe that our study provided a starting point for answering this question by showing improvement in depressed mood among demented patients, but much work remains to be done in determining exactly how best to achieve this. In response to these letters, I would like to offer the following general observations.

1. I think that it would be premature to reject the use of tricyclic antidepressants in this population, if for no other reason than the fact that some patients strongly believe in and prefer pharmacologic therapy, and we have no basis for saying nonpharmacologic treatment is superior.

2. The choice of imipramine as our pharmacologic intervention was a judgment call and was not meant to imply any specificity for imipramine in this condition.

3. It is my subjective opinion that a larger dose of imipramine would not have caused any substantial additional improvement in depressive symptoms but probably would have produced greater problems with drug toxicity. I agree that it is important to test this opinion empirically, but the aforementioned subjective impression dampens my enthusiasm for doing this myself.

BURTON V. REIFLER, M.D., M.P.H.
Winston-Salem, N.C.

Neuroleptic-Induced Dystonia

SIR: The report "Higher Frequency of Neuroleptic-Induced Dystonia in Mania Than in Schizophrenia" (1) was read by us with interest. The hypothesis that patients with affective disorders are more likely to develop acute dystonias following treatment with neuroleptic drugs is interesting and provocative. However, there are some problems with the study. Although acute dystonias are regarded as idiosyncratic, their occurrence also appears to be dose-dependent. The probability of occurrence of dystonia increases with increasing doses of neuroleptic drug (2, 3). Approximately 50% of acute dystonias occur within 48 hours and about 90% within 5 days of starting therapy (2, 4, 5). Therefore, it would be more relevant to describe the mean dose of neuroleptic used during the risk period for developing an acute dystonic reaction, i.e., during the first 96 hours after starting treatment with neuroleptics. In this report, the authors did not explain how the mean daily dose of neuroleptics used was calculated. The comparison of peak or maximum doses used daily for the first 96 hours (not the total mean dose, as described) in the manic and schizophrenic groups might help explain the higher prevalence of dystonia in the manic group. Was the dystonic group of patients more agitated and, thus, did they receive more parenteral neuroleptics than the non-dystonic group? The authors stated that both groups of patients had been treated predominantly with high-potency neuroleptics. It would be helpful to know the specific drugs and doses involved rather than dosage equivalents.

In a previous study (6), one of us (G.M.S.) reported that subjects who received high doses of a neuroleptic followed by a drug-free period of 35 days and then received a lower dose of the same neuroleptic suffered from more extrapyramidal symptoms the second time, with the lower dose. It was concluded that they had been sensitized to the neuroleptic. The intermittent treatment that manic patients receive

and also the brief high doses they receive may be responsible for this finding, rather than the disorder itself. It is possible that Dr. Nasrallah and associates have data to address some of these questions.

REFERENCES

1. Nasrallah HA, Churchill CM, Hamdan-Allan GA: Higher frequency of neuroleptic-induced dystonia in mania than in schizophrenia. *Am J Psychiatry* 1988; 145:1455-1456
2. Swett C Jr: Drug-induced dystonia. *Am J Psychiatry* 1975; 132: 532-534
3. Doongaji DR, Jeste DV, Jape NM, et al: Effects of intravenous metoclopramide in 81 patients with tardive dyskinesia. *J Clin Psychopharmacol* 1982; 2:376-379
4. Ayd FJ: A survey of drug-induced extrapyramidal reactions. *JAMA* 1961; 175:1054-1060
5. Garver DL, Davis DM, Dekirmenjian H, et al: Dystonic reactions following neuroleptics: time course and proposed mechanisms. *Psychopharmacologia* 1976; 47:199-201
6. Simpson GM, Laska E: Sensitivity to a phenothiazine (butaperazine). *Can Psychiatr Assoc J* 1968; 13:499-506

GEORGE M. SIMPSON, M.D.
HARDEEP SINGH, M.D.
Philadelphia, Pa.

Drs. Nasrallah and Churchill Reply

SIR: The comments of Drs. Simpson and Singh are thoughtful and well-taken. Retrospective studies are almost always flawed and not definitive because of missing data and problems arising from the uncontrolled, naturalistic design. However, such studies serve the useful purpose of crudely and quickly testing a hypothesis before one embarks on a rigorously designed, time-consuming, well-controlled prospective study.

The hypothesis tested in our study was based on the repeated mentions in the literature of the higher vulnerability of patients with affective disorders to tardive dyskinesia rather than on pharmacokinetic principles. Drs. Simpson and Singh are correct about the limitations of the study and about the potential usefulness of additional data in confirming alternative hypotheses regarding neuroleptic-induced mania in acutely psychotic populations. We regret that the data they are interested in were not recorded in a manner that would permit reanalysis, and we have moved to another institution. We are currently planning a prospective clinical study of bipolar patients and schizophrenia, and we hope that other investigators such as Drs. Simpson and Singh will also conduct studies in this area to test alternative hypotheses, including sensitization by previous neuroleptic treatment(s).

HENRY A. NASRALLAH, M.D.
CYNTHIA M. CHURCHILL, M.D.
Columbus, Ohio

Empathy and Schizophrenia

SIR: We enjoyed the article by Leslie Brothers, M.D., in which she presented a biological perspective on empathy (1). She described several clinical pathological syndromes that display an impairment of empathy, including infantile autism, alexithymia, and certain neurological syndromes.

A neurobiological understanding of empathy may also be

relevant to schizophrenia. Many of the attributes defining the schizoid personality, as well as the deterioration of personality found in some chronic schizophrenic patients, seem to overlap with empathy. These personality impairments were first described by Kraepelin and Bleuler.

Dr. Brothers discussed several late nineteenth- and early twentieth-century influences on the developing concept of empathy. In addition to the psychoanalytic study of empathy, the phenomenological approach of Husserl was adapted for application in clinical psychopathology by Jaspers. In developing psychopathology as a scientific discipline, Jaspers stressed two processes whereby clinicians gain knowledge of the experience of others: the cognitive process of language and the empathic emotional process. The break in empathy was viewed as a cardinal feature of schizophrenia, accounting for one's inability to understand certain of the experiences of schizophrenia. The primacy of this lack of understanding gained its greatest influence in the Schneiderian diagnostic approach, but this was a prevailing influence throughout the German phenomenological school of psychiatry.

Certain research on schizophrenia also relates to the concept of empathy. The International Pilot Study of Schizophrenia found that poor rapport strongly distinguished patients with schizophrenia from patients with other psychotic disorders (2). Schizophrenic persons also appear to have an impairment in the cognitive processing of human faces (3). The concept of empathy also overlaps with the impairments used to define putative negative symptom subtypes. There have been a number of attempts to delineate putative schizophrenic subtypes defined by these personality attributes, including a recent discussion in the *Journal* (4) of the deficit syndrome.

We have developed elsewhere (manuscript by Kirkpatrick and Buchanan under review) the argument that damage to the putative neural circuit subserving social affiliation (5) underlies the deficit syndrome. This circuit includes the amygdala—perhaps, especially, the basolateral amygdala. This functional circuit appears to have common functions in a number of mammalian species, including humans, primates, and nonprimates.

Dr. Brothers' article encourages further work in this area. We hope she will comment on the role of empathy in schizophrenia.

REFERENCES

1. Brothers L: A biological perspective on empathy. *Am J Psychiatry* 1989; 146:10-19
2. Carpenter WT Jr, Strauss JS, Bartko JJ: A flexible system for the diagnosis of schizophrenia: a report from the International Pilot Study of Schizophrenia. *Science* 1973; 182:1275-1278
3. Morrison RL, Bellack AS, Mueser KT: Deficits in facial-affect recognition and schizophrenia. *Schizophr Bull* 1988; 14:67-84
4. Carpenter WT Jr, Heinrichs DW, Wagman AMI: Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry* 1988; 145:578-583
5. Kling A, Steklis HD: A neural substrate for affiliative behavior in nonhuman primates. *Brain Behav Evol* 1976; 13:216-238

BRIAN KIRKPATRICK, M.D.
WILLIAM T. CARPENTER, JR., M.D.
ROBERT W. BUCHANAN, M.D.
Baltimore, Md.

Dr. Brothers Replies

SIR: I appreciate the thoughtful letter of Dr. Kirkpatrick and associates regarding the role of empathy in schizophrenia.

Empathy should perhaps be considered as part of a larger functional sphere, that is, the sphere of social cognition. The idea that there is such a faculty was articulated by Gardner (1), who adduced clinical syndromes such as autism as evidence for its discreteness, and has been interestingly rearticulated by Jackendoff (2). The presence of other deficits besides that of empathy in autistic children, especially disturbances of language pragmatics and social gesturing, argues for this view. I am suggesting, in other words, that it may be useful to have a broader concept of what is awry in the social functioning of schizophrenic persons than impairment of empathy.

In spite of the considerable evidence implicating the brain structures thought to subserve social communication in the pathology of schizophrenia, I do not believe that even certain schizophrenic deficit syndromes can functionally dissect the social cognitive system for us. The reason is that medial temporal structures almost certainly play a role in nonsocial mentation as well. However, if a valid deficit subtype can be demonstrated and then correlated with damage to these structures, additional light might be shed on their functions. In this regard it is interesting that features of the deficit subtype proposed by Carpenter et al. (3) are the same as those cited by Bear et al. for chronic temporal lobe epilepsy (4), but in the opposite direction. For example, Bear et al. described deepened emotionality and social clinging. The hypergraphia of temporal lobe epilepsy patients may result from a greater intensity and amount of ideation—again, the inverse of the characteristics of Carpenter et al.'s deficit population.

A well-known difficulty is that even when there is evidence of alteration in a particular structure, we cannot rule out the presence of other more diffuse dysfunctions of neural operations. A diffuse derangement of higher cognitive function would be expected to show up prominently in the sphere of social cognition simply because in a world full of other people, social cognition is often engaged. Thus, schizophrenic patients with prominent social impairments usually have impairments in other spheres as well, for example, in the use of language and in abstract thought.

Undoubtedly, the work to which Dr. Kirkpatrick and associates refer addresses the points I have raised. I look forward to seeing their full treatment of the relation between the deficit subtype and pathology of medial temporal structures.

REFERENCES

1. Gardner H: *Frames of Mind: The Theory of Multiple Intelligences*. New York, Basic Books, 1983, pp 237-276
2. Jackendoff R: *Consciousness and the Computational Mind*. Cambridge, Mass, MIT Press, 1987, pp 208-209
3. Carpenter WT Jr, Heinrichs DW, Wagman AMI: Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry* 1988; 145:578-583
4. Bear D, Levin K, Blumer D, et al: Interictal behaviour in hospitalised temporal lobe epileptics: relationship to idiopathic psychiatric syndromes. *J Neurol Neurosurg Psychiatry* 1982; 45:481-488

LESLIE BROTHERS, M.D.
Pasadena, Calif.

Children's Allegations of Sexual Abuse

SIR: Although some time has passed since the article "Preschool Children's Erroneous Allegations of Sexual Molestation" by Alayne Yates, M.D., and Tim Musty (1) appeared, I feel compelled to signal my great discomfort with the content of that article. Not one case mentioned involved any reasonable degree of certainty that these children's reports were false. It is clear that the children were subjected to a great deal of pressure by persons who already believed that lies had been told and that the children sometimes buckled under that pressure (and sometimes did not).

In no area of law or mental health is there complete certainty. The authors seem to believe that such certainty, or something approximating it, can be achieved if the therapist is just clever enough, devious enough, or "confrontational" enough. The central point here is that, in the realm of small children and alleged sexual abuse, there was until just the last few years a preference for "false negatives" (abuse that happened but was not believed by authorities) over "false positives" (abuse that is believed but did not occur). Even the authors admitted that the latter cases are quite rare with respect to the former, yet printing this article with this title serves to give undue emphasis to the alleged phenomenon of false claims of sexual abuse by very young children. This sort of media influence is congruent with this country's current shifting to the right (and far right) politically, in that the powerless (children) are not protected, but those with the resources (accused adults) are defended; I fear this growing preference for false negatives over false positives, "like the good old days."

I ponder the degree to which the authors have been able to identify with the very small and very powerless child within themselves. It is not the place of clinicians to pressure and trick children—particularly very young children—into saying what we (whether right or wrong) believe to be the truth. If anyone must pressure, confront, or otherwise threaten and harass preschoolers, let it not be us!

REFERENCE

1. Yates A, Musty T: Preschool children's erroneous allegations of sexual molestation. *Am J Psychiatry* 1988; 145:989-992

TERESA WHITEHURST, PH.D.
Norfolk, Va.

Dr. Yates Replies

SIR: Dr. Whitehurst is concerned that the children presented in our article could actually have been abused and that they were pressured into saying that they had lied about being abused. She is also worried that since we assumed that these children were not abused, we did not protect them from further abuse.

All but one of the children described in the article were scrutinized by a number of experts in the field. The examiners viewed these cases as exceptional, because they so seldom encountered children who seemed to be inaccurate in their descriptions. They accepted the children's reality as important, and in no case did they attempt to pressure the children to change their minds. In addition, even though the consensus of examiners and the court was that the children had not been abused, two of the children continued to be "protected"

from the accused parent. In the other two cases, the mothers realized that they had been mistaken, the issue was resolved, and visitation proceeded without incident.

It is our duty to protect children from various forms of abuse, including psychological abuse. If a parent persuades, tricks, or misleads a child, thus setting the child against the other parent, this can produce persistent anger, guilt, or sadness in the child at the loss of what is often a meaningful relationship. Although we may be able to empathize with the parent who honestly believes that he/she is justified in involving the child, the act is nonetheless abusive.

The issue of false negatives is important. For years the assumption was that sexual abuse seldom occurred and that any accusation must be a lie or be based on fantasy. As we stated in the article, there is good reason to believe children when they report sexual abuse. We agreed with other authors who emphasize that most apparently false accusations occur in the context of a highly charged custody or visitation dispute, where there is something to be gained by directly or indirectly casting aspersions.

The field of sexual abuse is bewildering in its complexity. The more we can avoid overgeneralizing, the more likely we are to maintain objectivity.

ALAYNE YATES, M.D.
Tucson, Ariz.

Stimulants, Panic, and BEAM EEG Abnormalities

SIR: Alan K. Louie, M.D., and associates' report (1) linking cocaine use with panic disorder is an important contribution to the hypothesis that certain forms of drug use predispose to certain psychiatric illnesses. Equally germane is evidence from animal research that pharmacological kindling occurs in a number of species when cocaine is given. However, to the best of my knowledge, no evidence to date, including my own discovery of abnormal brain electrical activity mapping (BEAM) in panic disorder (2, 3), has shown that pharmacological kindling occurs in humans. Consequently, some clarification is in order.

I used computerized BEAM and/or conventional EEG to study 15 panic patients. Eight patients had abnormal findings. Each of those eight had a history of stimulant abuse (cocaine, amphetamine, or LSD), whereas only one of the seven patients with normal BEAM findings had such a history ($p=0.003$). Cocaine had been abused by 50% of these eight subjects and LSD by 65.5%. Three of the eight also had comorbid diagnoses of posthallucinogen perception disorder (DSM-III-R). Therefore, according to these data, use of LSD may be as significant a forerunner of acquired panic as use of cocaine. This is in keeping with the observations of Dr. Louie and associates that six of their 10 patients had comorbid visual illusions, and five of those six had abused LSD. Accordingly, it would be interesting to know whether any of those patients fulfilled the criteria for posthallucinogen perception disorder.

Finally, among the 29 separate BEAM abnormalities in my sample, 28 were of auditory and visual evoked potentials and/or excess slow waves. Two-thirds of the BEAM abnormalities were symmetrically distributed in the temporal lobes. Only one patient had overt spike activity. In the absence of physiological evidence of seizure activity, one may be inclined to describe these electrical dysfunctions as temporal dysrhythmias rather than kindled seizures. This hardly

negates the hypothesis of pharmacological kindling in humans, as lucidly argued by Dr. Louie and his colleagues, and the consequent psychopathology, which perhaps arises from deeper limbic structures. This may be particularly true given the impairment in bilateral temporal lobe function that I found. Case-controlled studies are needed to clarify this highly suspicious link between stimulants, panic disorder, and electrical dysfunction of the temporal lobes.

REFERENCES

1. Louie AK, Lannon RA, Ketter TA: Treatment of cocaine-induced panic disorder. *Am J Psychiatry* 1989; 146:40-44
2. Abraham HD: Do psychostimulants kindle panic disorder? (letter). *Am J Psychiatry* 1986; 143:1627
3. Abraham HD: BEAM studies in panic disorder: an exploration, in CME Syllabus and Scientific Proceedings in Summary Form, 141st Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1988

HENRY DAVID ABRAHAM, M.D.
Boston, Mass.

Dr. Louie and Associates Reply

SIR: We reported that classical and cocaine-induced panic disorders differ in terms of symptoms, family history, and treatment response. Dr. Abraham's BEAM data further support this differentiation and suggest that classical and drug-induced panic disorders involve different pathophysiological mechanisms.

Dr. Abraham characterizes the BEAM abnormalities as bilateral temporal lobe dysrhythmias rather than frank seizure activity and raises questions concerning the kindled seizure hypothesis, which we had presented for cocaine-induced panic disorder. Arguments in support of the hypothesis would be that scalp electrodes may not detect spike activity in deep limbic structures and that such activity may be evident only during a panic attack.

Dr. Abraham also suggests that use of hallucinogens may be as important as use of cocaine in inducing panic disorder. We had some panic patients who abused cocaine but never hallucinogens, but none who did the opposite. Therefore, we did not have any cases in which hallucinogens alone were implicated. Six of our 10 patients had used hallucinogens in addition to cocaine. This was associated with a greater risk of having visual illusions during panic attacks. These patients did not strictly meet the *DSM-III-R* criteria for posthallucinogenic perception disorder.

ALAN K. LOUIE, M.D.
RICHARD A. LANNON, M.D.
TERENCE A. KETTER, M.D.
San Francisco, Calif.

Blood-Injury Phobia

SIR: The review article on blood-injury phobia by Isaac Marks, M.D., F.R.C.Psych. (1) provided a welcome update on a neglected topic. The differentiation between simple fears of blood and wounds (that do not result in fainting upon exposure) and their phobic correlates (with the characteristic biphasic response and familial history) was stressed. Little is

known, however, about the prevalence of fears of blood wounds, and injury in other psychiatric disorders (2).

Members of our group recently reported (3) on symptoms related to blood-injury phobia in 18 patients who had panic disorder with agoraphobia according to the *DSM-III-R* criteria. Symptoms were evaluated by both observer (4) and self-rating (5) methods. Patients rated themselves significantly higher than did healthy control subjects, matched for sociodemographic variables, on the blood-injury phobia subscale of the Fear Questionnaire (5). In 13 of the 18 patients and in one of the 18 control subjects, there was clear-cut avoidance of blood tests and hospitals, even though no patients reported that they fainted at the sight of blood, when injured, during dental procedures, or while watching violent movies. Fears of blood and injury improved with exposure treatment of the agoraphobia (3).

In another sample of 20 patients suffering from panic disorder with agoraphobia (6), fears of blood and wounds were present in only two of the patients before the occurrence of panic attacks, unlike patients with agoraphobia or social phobia. In both of these samples of patients with panic disorder (3, 6), no patients had first-degree relatives with clear-cut blood-injury phobia.

We recently also investigated the occurrence of blood-injury phobia in a sample of 15 patients (nine men and six women; mean age=45 years) with primary major depressive disorder according to the Research Diagnostic Criteria. On the observer ratings (4) only two of the 15 patients showed clear-cut avoidance of blood tests and hospitals. The findings suggest that fears of blood, wounds, and injury are rather common in panic disorder and are probably largely a secondary phenomenon which, indeed, improves with nonspecific treatment. The results of our studies are in agreement with other investigations of the relationship between agoraphobia and other phobic symptoms (2, 5) and have methodological implications for studies of the biology of panic disorder. Several such studies, in fact, use procedures involving blood collection. Patients may display anxiety and/or panic in response to blood collection more than to specific stimuli. If the studies are not placebo controlled, the presence of fears related to blood-injury phobia may yield spurious results in comparisons between patients with panic disorder and healthy control subjects or other psychiatric patients (e.g. depressed patients). The findings should alert investigators to use psychometric instruments, such as the Fear Questionnaire (5), to screen for blood-injury phobia and/or to control for its intensity in their studies on the biology of panic.

REFERENCES

1. Marks I: Blood-injury phobia: a review. *Am J Psychiatry* 1988; 145:1207-1213
2. Bowen R, Fischer DG, Barrett P, et al: The relationship between agoraphobia, social phobia and blood-injury phobia in phobic and anxious-depressed patients. *Can J Psychiatry* 1987; 32: 275-281
3. Fava GA, Grandi S, Canestrari R: Blood-injury phobia and panic disorder: a neglected relationship. *Med Science Research* 1988; 16:217-218
4. Paykel ES: The Clinical Interview for Depression. *J Affectiv Disord* 1985; 9:85-96
5. Marks IM, Mathews AM: Brief standard self-rating for phobic patients. *Behav Res Ther* 1979; 17:263-267
6. Fava GA, Grandi S, Canestrari R: Prodromal symptoms in

panic disorder with agoraphobia. *Am J Psychiatry* 1988; 145: 1564-1567

GIOVANNI A. FAVA, M.D.
SILVANA GRANDI, M.D.
FRANCESCO M. SAVIOTTI, M.D.
GIOVANNA BARTOLUCCI, M.D.
GIANNI SAVRON, M.D.
SANDRA CONTI, M.D.
Bologna, Italy

Dr. Marks Replies

SIR: Dr. Fava and associates draw attention to an interesting phenomenon, reports of blood-injury fears both in blood-injury phobic patients and in agoraphobic patients with panic. It would be important to investigate the cardiovascular response to the sight of blood; the incidence of vasovagal fainting; family history of blood-injury fears, agoraphobia, and other fears; and age at onset of these fears. It is fascinating that Dr. Fava and his colleagues did not find blood-injury fear in 15 depressed patients.

This topic has been neglected and deserves further investigation.

ISAAC MARKS, M.D., F.R.C.PSYCH.
London, England

Alprazolam and Aggression

SIR: Initial enthusiasm about the value of the triazolobenzodiazepine alprazolam in depressive as well as anxiety disorders has been tempered by concern over adverse effects (1). In addition to dependence and difficult withdrawal reactions, treatment-emergent symptoms such as hostility and aggression have been reported, particularly in patients with borderline personality disorder (2). In this context, the case recently described in the *Journal* by Alfred P. French, M.D. (3) is of particular interest. Intentionally taking approximately 10 mg of alprazolam (usual daily dosage not stated), Dr. French's patient slept for 8 hours, then engaged in progressively escalating violence, ranging from arguing with his wife and throwing rocks at their truck to driving recklessly toward pursuing police cars and struggling with a police officer after crashing.

As dramatic as this case was, we have serious misgivings about its validity for documenting a putative risk of the therapeutic use of alprazolam. The repeated use of the term "side effect" was misleading in a case report of an acute overdose of a drug. An important aspect of interpreting the patient's behavior is the extent of any delirium; no such information was provided, except for mental status 5 months later. In particular, we wonder about the history of recent amitriptyline use; could the patient have taken any remaining tricyclic medication as well as "all of the alprazolam available to him"? A toxic delirium is not uncommon in overdoses of strongly anticholinergic tricyclic antidepressants such as amitriptyline (4) and would probably be more likely to occur, even at a relatively low dose, in a patient with prior evidence of brain dysfunction, such as the one reported. Was blood or urine screening performed to document that, in fact, alprazolam was the only drug consumed before the reported episode? Our own experience with use of an acute intravenous bolus of alprazolam (up to 0.02 mg/kg) as a pharmacologic

probe (5) has so far elicited no aggressive outbursts, disorientation, or other evidence of organicity in either depressed patients or healthy volunteers.

Finally, as the field of psychopharmacology attempts to make optimal matches between specific medications and putative clinical and biochemical subtypes of psychiatric disorders, it is unfortunate to encounter cases published with impressionistic diagnostic labels such as "situational depression"—diagnosis according to the MMPI rather than *DSM-III-R*. Our clinical suspicion is that marital disputes settled with a baseball bat to the head (before alprazolam) tend to occur in the context of psychopathology beyond unipolar depression. In sum, while we do not want to minimize the real risks potentially associated with alprazolam treatment (1), in some patients its advantages (e.g., lack of anticholinergic effects and greater safety in overdose than with tricyclics) remain compelling, Dr. French's case notwithstanding.

REFERENCES

1. Rudorfer MV, Potter WZ: The new generation of antidepressants, in *Treatment of Tricyclic-Resistant Depression*. Edited by Extein IL. Washington, DC, American Psychiatric Press, 1989
2. Gardner DL, Cowdry RW: Alprazolam-induced dyscontrol in borderline personality disorder. *Am J Psychiatry* 1985; 142: 98-100
3. French AP: Dangerously aggressive behavior as a side effect of alprazolam (letter). *Am J Psychiatry* 1989; 146:276
4. Rudorfer MV, Robins E: Amitriptyline overdose: clinical effects on tricyclic antidepressant plasma levels. *J Clin Psychiatry* 1982; 43:457-460
5. Osman OT, Hsiao JK, Rudorfer MV, et al: Dose-response changes after acute alprazolam in normal volunteers (abstract 18), in *Abstracts of the 43rd Annual Meeting of the Society of Biological Psychiatry*. Los Angeles, SBP, 1988

MATTHEW V. RUDORFER, M.D.
OSSAMA T. OSMAN, M.D.
WILLIAM Z. POTTER, M.D., PH.D.
Bethesda, Md.

Dr. French Replies

SIR: Dr. Rudorfer and associates correctly point out that the report would have been improved by substitution of "acute toxic reaction" for "side effect," and they point out that further information would permit a higher level of certainty about whether alprazolam was the major cause of this man's life-threatening behavior.

The 1989 edition of the *Physicians' Desk Reference* states that benzodiazepines may cause irritability, agitation, memory impairment, and rage. Although these toxic effects are not attributed to alprazolam specifically, alprazolam is a benzodiazepine. The subject of my report informed me that he had taken an overdose of all available alprazolam, and the police and other reports adequately confirm his irritability, agitation, and rage. He reported memory impairment. I agree, of course, that a higher level of certainty is always better, that there are points in the report which invite question, and that this one report does not constitute a general attack on the usefulness of alprazolam in many individuals for whom it is uniquely suitable. However, I am sufficiently comfortable with the inference of a causal relationship between the reported overdose of alprazolam and this man's dangerous behavior to find the case suitable for a single case

report, particularly in view of the fact that the acute toxic effects of other benzodiazepines are precisely those seen here.

I am disappointed that Dr. Rudorfer and associates have not addressed a central issue in the matter: the possibility of the occurrence of such toxic effects as irritability and rage with alprazolam. It would have been helpful to learn in what circumstances these extremely dangerous toxic effects might reasonably be expected to occur.

This may have been a "false positive" report; one can always argue for more studies and for a higher level of certainty. However, I am shaken by the level of tragedy this young man so narrowly missed (death, serious injury, extensive burns, and decades of imprisonment) and hope that others will be sensitive to the possibility that alprazolam, like other benzodiazepines, may be extremely hazardous in some individuals.

ALFRED P. FRENCH, M.D.
Sacramento, Calif.

Problems of the Inpatient Unit Director

SIR: I was greatly impressed by the article "The Academic Dilemma of the Inpatient Unit Director" by Ellen Leibenluft, M.D., and associates (1). The authors concluded that "academic inpatient psychiatry suffers from an inability to attract and retain talented clinician-researchers as directors of inpatient units . . . [because] the directorship . . . is relegated to the most junior member of the faculty, who is then overloaded with responsibilities that preclude academic productivity."

Their very thoughtful discussion makes it abundantly clear that the authors are cognizant of the *clinical* expertise required of the director of an inpatient unit. Such expertise requires a thorough understanding and working knowledge of group dynamics, developmental issues, and psychoanalytic concepts such as transference. Referring to the work of Kernberg, Dr. Leibenluft and associates stated that the inpatient director becomes "the object of primitive, powerful patient and staff transferences." They also stated that perhaps not all academic psychiatrists should be full-time researchers.

I am sure that most, if not all, full-time clinicians agree with this conclusion. The removal of psychoanalysts from many academic departments, facilitated by the elimination of "half-time" positions, has contributed to the exodus of a pool of faculty members with long clinical experience. In the past, a half-time unit director could maintain a private practice, undergo analytic training, and then continue with the unit's directorship during his or her career as a psychoanalyst, as I myself did for a long period of time (2).

I view the article as indicative of the authors' perception of the problem in academic psychiatry: the distance it has gone from an interest in psychology toward an interest in biology. The "biopsychosocial model" is, in reality, a euphemism for "We psychiatrists take care of the 'biology' and the other mental health professionals take care of the psychological and social issues." Unfortunately, the leaders in academic psychiatry do not recognize that a graduating or recently graduated resident, with limited clinical experience, who becomes the leader of the "team" cannot lead such a team without adequate training in the workings of the mind. Academic psychiatry would do well

to create a rapprochement with psychoanalysis to reinvigorate the clinical training of its residents.

REFERENCES

1. Leibenluft E, Summergrad P, Tasman A: The academic dilemma of the inpatient unit director. *Am J Psychiatry* 1989; 146:73-76
2. Hoffman L (ed): *The Evaluation and Care of Severely Disturbed Children and Their Families*. New York, Spectrum, 1982

LEON HOFFMAN, M.D.
New York, N.Y.

Dr. Leibenluft and Associates Reply

SIR: We thank Dr. Hoffman for his thoughtful comments regarding the importance of clinical psychodynamic and psychoanalytic training for the work of the inpatient director. Dr. Hoffman's letter serves to highlight some of the other skills that the inpatient director needs to function successfully.

While we would agree that inpatient directors need to be experts in a variety of psychodynamic concepts, they likewise require sophistication in other arenas, including neuropsychiatric evaluation, psychopharmacologic management, medical/psychiatric interactions, and an array of management tasks in this era of intense regulation of hospital expenditures. When one adds to that list the expectation of academic productivity, the task of the inpatient director, we believe, becomes formidable.

We do not disagree with Dr. Hoffman that inpatient directors need clinical, including psychodynamic, expertise. We do think, however, that it is critical that all areas of psychiatric practice and research undergo at least some degree of structured, formal evaluation and research. Such work has been done for many psychiatric practices, including psychotherapy and psychoanalysis (1) and, to some degree, inpatient psychiatric services (2). Given the money and time that are spent on inpatient psychiatric care, we think it is important to develop a cadre of senior clinician-investigators who can study the efficacy of such treatment.

REFERENCES

1. Luborsky L, Crits-Christoph P, Mintz J, et al: *Who Will Benefit From Psychotherapy?* New York, Basic Books, 1988
2. Lieberman PB, Strauss JS: Brief psychiatric hospitalization: what are its effects? *Am J Psychiatry* 1986; 143:1557-1562

ELLEN LEIBENLUFT, M.D.
Bethesda, Md.
PAUL SUMMERGRAD, M.D.
Boston, Mass.
ALLAN TASMAN, M.D.
Farmington, Conn.

Correction

In the letter to the Editor "Refinement of the Diagnosis of Schizophreniform Disorder" from Patrick E. Ciccone, M.D. (April 1989 issue, pp. 561-562), the question in the first line of the last paragraph should begin "is it not reasonable . . . ?"

Reprints of letters to the Editor are not available.



**A spectrum of reasons
to write D.A.W.
when you prescribe**



Norpramin[®]

10, 25, 50, 75, 100, 150 mg

(desipramine hydrochloride tablets USP)

A logical choice among antidepressants

A 25-year history of proven clinical usefulness with unsurpassed **flexibility of dosage** provided by 6 tablet strengths, **color coded** to ensure exact identification. It also offers **dose equivalence** that permits prescribing one tablet of greater strength in place of multiple doses of lesser strengths, resulting in **increased patient compliance** and greater than **20% cost savings**.

Merrell Dow U.S.A.

(Brief Summary of Prescribing Information appears on the next page.)



Ensure the maximum benefits of Norpramin by specifying "Dispense As Written."

- A 25-year record of efficacy in relieving the symptoms of depression*
- Less anticholinergic activity than amitriptyline or doxepin*
- Usually no excessive daytime drowsiness (see Warnings)†

Norpramin (desipramine hydrochloride tablets USP)

*References supporting these statements available from MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242.

†Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

Merrell Dow U.S.A.
Division of Merrell Dow Pharmaceuticals Inc.

Norpramin®

10, 25, 50, 75, 100, 150 mg
(desipramine hydrochloride tablets USP)

Norpramin® (desipramine hydrochloride tablets USP)

BRIEF SUMMARY

CAUTION: Federal law prohibits dispensing without prescription.

INACTIVE INGREDIENTS

The following inactive ingredients are contained in all dosage strengths: acacia, calcium carbonate, corn starch, D&G Red No. 30 and D&G Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Metabolism

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Additional information on metabolism appears in Full Prescribing Information.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

1. Extreme caution should be used when this drug is given in the following situations:
 - a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
 - b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
 - c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
 - d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. **USE IN PREGNANCY**
Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**
Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdose.

PRECAUTIONS

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be mentioned when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. There has been a report of an "acute collapse" and

"sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity. (See WARNINGS, Use in Children.)

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure, constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evacuation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here. Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

(a) Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dose. In vitro experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.

(b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levarterenol and metaraminol, they should be used only with caution.

(c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.

(d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

Product Information as of January, 1989

Y398D

MERRELL DOW U.S.A.
A Division of Merrell Dow Pharmaceuticals Inc.
Cincinnati, Ohio 45215

Merrell Dow U.S.A.

NOW AVAILABLE!
THE 5 mL MULTI-DOSE VIAL

- ☐ same 50 mg/mL concentration
- ☐ cost-effective
- ☐ increased convenience

For the schizophrenic patient

**Sustained drug levels
with a single monthly dose**

HALDOL[®] DECANOATE
(HALOPERIDOL) INJECTION

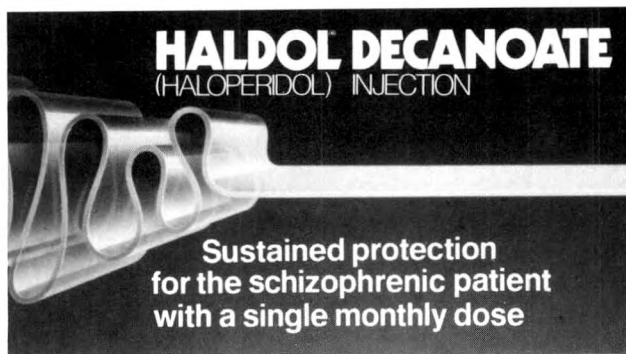
**Sustained protection
from relapse**

Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL[®] (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

 **McNEIL
PHARMACEUTICAL**
McNEILAB, INC., Spring House, PA 19477

© McNEILAB, INC., 1989



**Sustained protection
for the schizophrenic patient
with a single monthly dose**

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with the syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacologic treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinsonian medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intracranial pressure may increase when anticholinergic drugs, including antiparkinsonian drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL. The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause

allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; in 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. **Withdrawal Emergent Neurological Signs—Abrupt discontinuation** of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. **Tardive Dyskinesia—As** with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents should be discontinued if these symptoms appear. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that the fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. **Tardive Dystonia—Tardive dystonia**, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. **Other CNS Effects—Insomnia**, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) **Cardiovascular Effects:** Tachycardia, hypotension, hypertension and ECG changes. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Special Senses:** Cataracts, retinopathy and visual disturbances. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

7/20/88

**McNEIL
PHARMACEUTICAL**
McNEILAB INC. Spring House, PA 19477

In Tourette Syndrome

ORAPTM

(pimozide) Tablets

Helps Patients Be Themselves*

- **Excellent Symptom Control**

"Pimozide produced significantly more improvement of symptoms and less akinesic adverse effects than haloperidol. ... Improvement of 70% or more was reported by 74% of patients on pimozide compared with 45% on haloperidol ($p < .02$), and 84% rated pimozide better overall than haloperidol."¹

- **Significantly Less Sedation than Haloperidol**

In a double-blind, placebo-controlled study, "Pimozide was associated with lethargy or tiredness on significantly fewer days than haloperidol ($p < .01$), and this was reflected in greater immediate and long-term patient acceptance...."²

- **Documented Clinical Experience**

Pimozide has been used in the treatment of Tourette Syndrome for over 10 years.¹

- **Now Available from LEMMON**

For more information on ORAP, call 1-800-523-6542, extension 246; in Pennsylvania call collect, (215) 723-5544.

The Less Sedating Therapy for Tourette Syndrome

* ORAP is indicated for patients who have failed to respond satisfactorily to standard treatment. Please see following page for a brief summary of prescribing information.

LEMMON

© LEMMON COMPANY, SELLERSVILLE, PA 18960

ORAP™ The Less Sedating Therapy for Tourette Syndrome

(pimozide) Tablets

INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment of tics that are merely annoying or cosmetically troublesome. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 8 and 53 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

- ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than those associated with Tourette's Disorder.
- ORAP should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (e.g., penicillins, methylphenidate and amphetamines) and such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
- Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
- ORAP is contraindicated in patients with severe local central nervous system depression or comatose states from any cause.
- ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following: (see also PRECAUTIONS—Information for Patients).

Tardive Dyskinesia: A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rule out prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is extended. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that: 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS—Information for Patients.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal syndrome complex sometimes related to antipsychotic drugs. Clinical manifestations of NMS are hyperreflexia, rigidity, altered mental status (including cataplexy) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reinitiation of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hypersensitivity: Not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Other: Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a tumorigenic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS—Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General: ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidney.

Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concomitantly.

Laboratory Tests: An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QT interval beyond an absolute limit of 0.47 seconds (male) or 0.52 seconds (female), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency, secondary to diuretics, diuretics, or other causes, should be corrected before ORAP therapy is initiated and serum potassium maintained during therapy.

Drug Interactions: Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such

as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS).

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, anesthetics, and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors in males and females.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about three times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors in mice is not known.

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic adrenalectomy of an antipsychotic also causes elevated prolactin levels in humans. These data suggest that approximately one-third of human breast cancers are prolactin-dependent in origin, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although data suggest that such as galactorrhea, amenorrhea, gynecomasia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the results of these results are unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains. In the mouse dominant lethal test or in the micronucleus test in rats.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, as effect also produced by other antipsychotic drugs.

Pregnancy Category C: Reproductive studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, the multiple of the human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryofetal loss including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks.

Labor and Delivery: This drug has no recognized use in labor or delivery.

Nursing Mothers: It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in breast milk and because of the potential for teratogenicity and subsequent cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited.

Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder.

ADVERSE REACTIONS

General: Extrapyramidal Reactions: Neuroleptic (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported infrequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuroleptic reactions (acute dystonia, dyskinesia, akathisia, hyperreflexia, cataplexy, oculogyric crisis) have been reported far less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of anticholinergic drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be helpful for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal/Discontinuation Syndrome: Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the risk of occurrence of withdrawal emergent neurological signs but such further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

Tardive Dyskinesia: ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. If the symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; anticholinergic agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstate treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be treated.

It has been reported that the ventricular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

Electrocardiographic Changes: Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizures have occurred at doses above 20 mg/day.

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS).

Hypersensitivity: Hypersensitivity has been reported with other antipsychotic drugs.

Clinical Trials: The following adverse reaction tabulation was derived from 20 patients in a 6 week long placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	5	1
Diarrhea	1	0
Nausea	0	2
Vomiting	0	1
Constipation	4	2
Erythema	0	1
Thirst	1	0
Appetite Increase	1	0

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Slooped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Insomnia	2	2
Dizziness	0	0
Ataxia	8	0
Rigidity	2	0
Speech disorder	2	0
Head/neck change	1	0
Albino	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior effect	5	0
Special Sense		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes to light	1	0
Decreased accommodation	4	1
Spots before eyes	0	1
Urgeal Impotence	3	0

Because clinical investigation experience with ORAP in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

Other Adverse Reactions: In addition to the adverse reactions listed above, those listed below have been reported in U.S. clinical trials of ORAP in conditions other than Tourette's Disorder.

Body as a Whole: Asthenia, chest pain, periorbital edema
Cardiovascular/Respiratory: Postural hypotension, hypertension, hypertension, tachycardia, palpitations
Gastrointestinal: Increased salivation, nausea, vomiting, anorexia, GI distress
Endocrine: Loss of libido
Metabolic/Nutritional: Weight gain, weight loss
Central Nervous System: Dizziness, tremor, parkinsonism, blurring, dyskinesia
Psychiatric: Excitement
Skin: Rash, sweating, skin irritation
Special Senses: Blurred vision, cataracts
Urogenital: Retarded urinary frequency
Postmarketing Reports: The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ORAP.
Hematologic: Hemolytic anemia

OVERDOSEAGE

In general, the signs and symptoms of overdose with ORAP (pimozide) would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) electrocardiographic abnormalities, 2) severe extrapyramidal reactions, 3) hypotension, 4) a comatose state with respiratory depression.

In the event of overdose, gastric lavage, establishment of a patent airway and, if necessary, mechanically-assisted respirations are advised. Electrocardiographic monitoring should commence immediately and continue until the ECG parameters are within the normal range. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as norepinephrine, phenylephrine and naphazoline. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinsonian medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdose.

DOSEAGE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on the manifestations in Tourette's Disorder patients below the age of twelve are not available. Consequently, the suppression of tics by ORAP requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the risk of adverse effects are balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS—Laboratory Tests).

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whether or not tics persist at the level and extent first identified. In attempts to reduce the dosage of ORAP, consideration should be given to the possibility that increases of tic intensity and frequency may represent a transient, withdrawal related phenomenon rather than a relapse of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal is recommended in any case.

HOW SUPPLIED

ORAP (pimozide) 2 mg tablets, white, scored, imprint "LEMMON" and "ORAP 2—NDC 0093-0187-01, bottles of 100.

Dispense in light-resistant containers as defined in the official compendia.

Made in Canada

Manufactured by:
 McKel-Thermaceutical, (Canada) Ltd.
 Stouffville, Ontario L4A 7J7

Printed in USA
 Rev. A 6/86

Manufactured for:
 LEMMON COMPANY
 Sellersville, PA 19380

LEMMON
 © 1988 LEMMON COMPANY

1. Shapiro AK et al: *Pediatrics* 79:1032-1038, 1987.
 2. Ross MS et al: *Am J Psychiatry* 135:585-587, 1978.

THE BRITISH JOURNAL OF PSYCHIATRY

MAY 1989

VOLUME 154

Review Articles

- The impact of molecular genetics on our understanding of the psychoses.
M.J. Mullan and R.M. Murray 591
- Dementia and Parkinson's disease. *W.R.G. Gibb* 596

Comment

- Community care and the difficult and offender patient. *T.D. Scannell* 615

Papers

- The Glasgow rehabilitation survey. *M.G. Livingston and A. Bryson* 620
- Community management of schizophrenia. A two-year follow-up of a behavioural intervention with families. *N. Tarrier, C. Barrowclough, C. Vaughn, J.S. Bamrah, K. Porceddu, S. Watts and H. Freeman* 625
- Family history and cerebral ventricular enlargement in schizophrenia: a case control study. *M.J. Owen, S.W. Lewis and R.M. Murray* 629
- A study of factors associated with response to electroconvulsive therapy in patients with schizophrenic symptoms. *D. Dodwell and D. Goldberg* 635
- A family study of two subgroups of schizoaffective patients. *M. Maj* 640
- A comparison of in-patient and out-patient prescribing. *D.N. Anderson* 644
- The relationship between depression and hopelessness. Implications for current theories of depression. *S.M. Greene* 650
- The hormonal environment of post-natal depression. *B. Harris, S. Johns, H. Fung, R. Thomas, R. Walker, G. Read and D. Riad-Fahmy* 660
- Depression following spinal cord injury: a prospective in-patient study. *F.K. Judd, J. Stone, J.E. Webber, D.J. Brown and G.D. Burrows* 668
- A rating scale for drug-induced akathisia. *T.R.E. Barnes* 672
- Quality of parenting in alcoholics and narcotic addicts. *E. Bernardi, M. Jones and C. Tennant* 677
- Anorexia nervosa in Hong Kong. Why not more in Chinese? *S. Lee, H.F.K. Chiu and C. Chen* 683
- 'Asneezia'—some further observations. *G.D. Shukla* 689

Case Conference

- Thirty years' war: a battle with insomnia. *J.R. Newton, C. Shapiro and A. Stewart* 691

Point of View

- The damnation of benzodiazepines. *F. Kräupl Taylor* 697

Brief Reports

- The occurrence of depression following mania: a method of predicting vulnerable cases. *C.P. Lucas, J.C. Rigby and S.B. Lucas* 705
- Alexithymia, masked depression and loss in a holocaust survivor. *R.Z. Fisch* 708
- Two cases of agranulocytosis on addition of a butyrophenone to a long-standing course of phenothiazine treatment. *A.H. Young and R. Kehoe* 710
- Cholinergic syndrome following anticholinergic withdrawal in a schizophrenic patient abusing marijuana. *R. Tandon, D. Dutchak and J.F. Greden* 712
- De Clérambault's syndrome (erotomania) in organic delusional syndrome. *Y.Y. El Gaddel* 714
- Delusions of pregnancy in men. Case report and review of the literature. *S.K. Chaturvedi* 716

Correspondence

- A hundred years ago. *Researched by Henry Rollin* 719

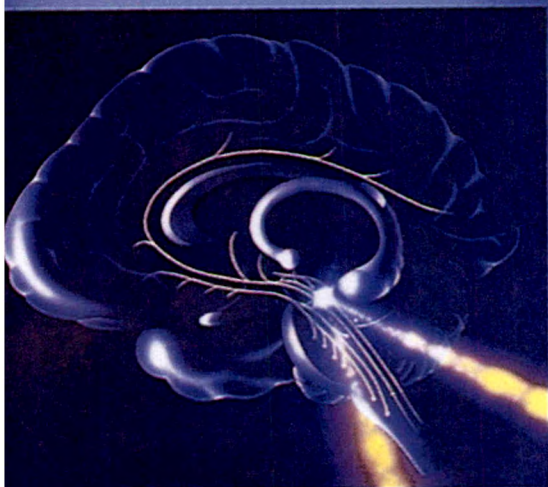
Books Reconsidered

- A critical dictionary of psychoanalysis. *C. Rycroft* 734

Book Reviews

738

The synapse—crossroads for serotonin



In depression

PROZAC[®]

fluoxetine hydrochloride

**'a potent serotonin reuptake inhibitor..
represents a new class
of antidepressants'¹**

Effectively relieves depression*

Unlike the tricyclics, Prozac specifically inhibits serotonin uptake. Its minimal action on other neurotransmitters may explain its favorable side-effect profile.

Fewer side effects to disrupt therapy

Side effects are generally mild and manageable, and include nausea, anxiety/nervousness, insomnia, and drowsiness

Avoid using MAO inhibitors concomitantly or in proximity to Prozac

Rash and/or urticaria occurred in 4% of clinical trial patients

A wide margin of safety

20-mg once-a-day therapy

PROZAC...
***A specifically different
antidepressant***



1. *Curr Ther Res* 1986;39:559-563.
*As defined by DSM-III.

*See adjacent page
for brief summary of
prescribing information.*

Prozac®

fluoxetine hydrochloride

Brief Summary: Consult the package literature for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindication: Prozac is contraindicated in patients known to be hypersensitive to it.

Warnings: Monoamine Oxidase Inhibitors—Data on the effects of the combined use of fluoxetine and MAOI inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAOI inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, conjunctival syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered varioliform to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of an idiosyncratic or pathogenic, is unknown at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: General—Anxiety and Insomnia—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately double that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo- and 3% of tricyclic antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Sedation—The possibility of a related tendency to increase in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see Clinical Pharmacology and Dosage and Administration).

Use in Patients with Concomitant Illness—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advised in using Prozac in patients with diseases or conditions that could affect metabolic or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Coagulation and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or fever.

Laboratory Tests—There are no specific laboratory tests recommended.

Drug Interactions—As with all drugs, the potential for interaction by a variety of mechanisms (i.e., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility (see Accumulation and Slow Elimination under Clinical Pharmacology).

Tryptophan—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors—See Warnings.

Other Antidepressants—There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (see Accumulation and Slow Elimination under Clinical Pharmacology).

Discontinuation—The half-life of concurrently administered diazepam may be prolonged in some patients (see Accumulation and Slow Elimination under Clinical Pharmacology).

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (see Accumulation and Slow Elimination under Clinical Pharmacology).

CNS-Active Drugs—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (see Accumulation and Slow Elimination under Clinical Pharmacology).

Epileptogenicity—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac. The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Use in Children—Safety and effectiveness in children have not been established.

Use in the Elderly—Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Hypotension—Several cases of hypotension (some with serum sodium lower than 110 mmol/L) have been reported. The hypotension appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Adverse Reactions: Commonly Observed—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The most common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.3%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

TABLE 1. TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event		Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Prozac (N=1,730)	Placebo (N=799)		Prozac (N=1,730)	Placebo (N=799)
Nervous			Body as a Whole		
Headache	20.3	15.5	Ataxia	4.4	1.9
Nervousness	14.9	8.5	Infection, viral	3.4	3.1
Insomnia	13.8	7.1	Pain, limb	1.6	1.1
Drowsiness	9.6	5.8	Fever	1.4	—
Anxiety	9.4	5.5	Pain, chest	1.3	—
Tremor	7.9	2.4	Allergy	1.2	1.1
Dizziness	5.7	3.3	Indigestion	1.2	1.6
Fatigue	4.9	1.1			
Sweating	1.9	1.3	Respiratory		
Upper					
Disturbance	1.7	2.0	Respiratory		
Libido, decreased	1.6	—	Infection	7.6	6.0
Light-headedness	1.6	—	Flu-like	2.8	1.9
Headache	1.6	—	Pharyngitis	2.7	1.3
Concentration, decreased	1.5	—	Nasal congestion	2.6	2.3
Digestive					
Nausea	21.1	10.1	Headache, severe	2.3	1.8
Diarrhea	12.3	7.0	Sinusitis	2.1	2.0
Mouth dyspraxia	9.5	6.0	Cough	1.6	1.8
Anorexia	8.7	1.5	Dyspnea	1.4	—
Dyspepsia	6.4	4.3	Cardiovascular		
Constipation	4.5	3.3	Hot flashes	1.9	1.0
Autonomic			Phlebotomy	1.3	1.4
Pain, back	3.4	2.9	Musculoskeletal		
Pain, joint	2.4	1.3	Pain, back	2.0	2.4
Taste change	1.8	—	Pain, joint	1.2	1.1
Flatulence	1.8	1.1	Pain, muscle	1.2	1.0
Gastroenteritis	1.0	1.4	Genitourinary		
Sexual			Interstition, penile	1.9	1.4
Erection, decreased	—	—	Swelling	—	—
Sexual			Dysfunction	1.9	—
Erection, excessive	8.4	3.8	Frequent	—	—
Rash	2.7	1.8	Urinary tract	1.6	—
Pruritus	2.4	1.4	Infection	1.2	—
			Special Senses		
			Vision		
			Disturbance	2.6	1.8

*Events reported by at least 1% of Prozac-treated patients are included.

—Incidence less than 1%.

Incidence in Controlled Clinical Trials—Table 1 enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigations. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Other Events Observed During the Premarketing Evaluation of Prozac—During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Unwanted events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of unwanted events into a limited (i.e., reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited at least on one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole—Frequent: chills; infrequent: chills and fever, cyst, face edema, hives, low back pain, malaise, neck pain, neck rigidity, and pelvic pain; Rare: abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System—Infrequent: angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; Rare: AV block (first-degree), bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Endocrine System—Frequent: increased appetite; infrequent: aphthous stomatitis, dysphagia, eruption, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melasma, stomatitis, and thirst; Rare: bloody diarrhea, cholelithiasis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperkalemia, increased salivation, jaundice, liver tenderness, mild urogenital, salivary gland enlargement, stomach ache, tongue discoloration, and tongue edema.

Endocrine System—Infrequent: hypothyroidism; Rare: goiter and hyperthyroidism.

Hemic and Lymphatic System—Infrequent: anemia and lymphadenopathy; Rare: bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, pancytopenia, purpura, sedimentation rate increased, and thrombocytopenia.

Metabolic and Nutritional—Frequent: weight loss; infrequent: generalized edema, hypoglycemia, peripheral edema, and weight gain; Rare: dehydration, gout, hypercholesterolemia, hyperglycemia, hypokalemia, hypophosphatemia, hypocalcemia, hypomagnesemia, and iron deficiency anemia.

Musculoskeletal System—Infrequent: arthritis, bone pain, bursitis, tenosynovitis, and twitching; Rare: bone necrosis, chondrodysplasia, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System—Frequent: abnormal dreams and agitation; infrequent: abnormal gait, acute brain syndrome, ataxia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, comedication, delirium, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperhidrosis, hyperreflexia, incoordination, libido increased, manic reaction, neuritis, neuropathy, parosmia, parosmia, psychosis, and vertigo; Rare: abnormal electroencephalogram, anticholinergic reaction, chorea, choreiform syndrome, circumoral paresthesia, CNS depression, convulsions, dysrhythmia, dystonia, extrapyramidal syndrome, hyperreflexia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and vertigo.

Respiratory System—Frequent: bronchitis, rhinitis, and yawn; infrequent: asthma, epistaxis, hiccup, hyperventilation, and pneumonia; Rare: apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/atelectasis, and pleural effusion.

Skin and Appendages—Infrequent: acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; Rare: eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, photosensitivity, pruritic rash, pustular rash, seborrhea, skin discoloration, skin hyper trophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses—Infrequent: amblyopia, conjunctivitis, ear pain, eye pain, myopia, photophobia, and strabismus; Rare: blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System—Infrequent: abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, hirsutism, breast impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; Rare: abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, polydipsia, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postmarketing Reports—Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after drug withdrawal, hyperprolactinemia, and thrombocytopenia.

Overdosage: Human Experience—As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of meprobamate. Plasma concentrations of fluoxetine and meprobamate were 4.57 mg/L and 4.18 mg/L, respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; citalopram, 1.80 mg/L; meprobamate, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (see Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent symptoms of overdose involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residual.

PI 2472 DFP

(11/7/88)

Additional information available to the profession on request from



Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46285

Prozac® (fluoxetine hydrochloride, Dista)

Prozac® (fluoxetine hydrochloride, Dista)

Prozac® (fluoxetine hydrochloride, Dista)

TRUST 35 YEARS OF PROVEN EXPERIENCE

THORAZINE[®]

brand of
chlorpromazine

See adjacent page for brief summary
of prescribing information.

SK&F

Smith Kline & French Laboratories

© SmithKline Beckman Corporation, 1989

THORAZINE®

brand of
chlorpromazine

See complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Contraindications: Comatose states or presence of large amounts of C.N.S. depressants.

Warnings: The possibility of extrapyramidal reactions from chlorpromazine may confuse the diagnosis of Reye's syndrome or other encephalopathy. Therefore, avoid use in children or adolescents with suspected Reye's syndrome.

May cause persistent tardive dyskinesia, which appears to be irreversible in some patients. Reserve chronic neuroleptic treatment for patients with chronic illness 1) that is known to respond to neuroleptics and 2) for whom there are no safer but equally effective treatment options. Use the smallest effective dose over the shortest treatment duration. If signs and symptoms of tardive dyskinesia develop, consider discontinuing the neuroleptic. A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. To manage NMS 1) discontinue immediately antipsychotic drugs and any other drugs not essential to concurrent therapy; 2) treat symptoms intensively and monitor; 3) where possible, treat serious concomitant medical problems. If antipsychotic treatment is needed after recovery from NMS, consider reintroducing drug therapy and monitor the patient carefully as recurrences of NMS have been reported. 'Thorazine' ampules and vials contain sodium bisulfite and sodium sulfite; the sulfite may cause allergic reactions, including anaphylactic symptoms. In patients with bone marrow depression or previously demonstrated hypersensitivity (e.g., blood dyscrasias, jaundice) with phenothiazines, do not administer 'Thorazine' unless the potential treatment benefits outweigh the possible hazards. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days therapy. Avoid concomitant use with alcohol. May counteract antihypertensive effect of guanethidine and related compounds. Use in pregnancy only when essential. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborns whose mothers had received chlorpromazine. Chlorpromazine is excreted in the breast milk of nursing mothers.

Precautions: Advise patients and/or guardians of the risk of tardive dyskinesia from chronic therapy. Use cautiously in persons with cardiovascular, liver or chronic respiratory disease, or with acute respiratory infections. Patients with a history of hepatic encephalopathy due to cirrhosis have increased sensitivity to the C.N.S. effects of chlorpromazine. Due to cough reflex suppression, aspiration of vomitus is possible. May prolong or intensify the action of C.N.S. depressants, organophosphorus insecticides, heat, atropine and related drugs. (Reduce dosage of concomitant C.N.S. depressants.) Anticonvulsant action of barbiturates is not intensified.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one-third of human breast cancers are prolactin-dependent *in vivo*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in glaucoma patients. May diminish the effect of oral anticoagulants, produce α -adrenergic blockade, and lower the convulsive threshold; dosage adjustment of anticonvulsants may be required. May interfere with Dilantin® metabolism, causing 'Dilantin' toxicity. May cause false positive phenylketonuria test results. Do not use with Ampaque®†. Discontinue 'Thorazine' at least 48 hours before myelography, do not resume for at least 24 hours postprocedure, and do not use to control N/V prior to myelography or postprocedure with 'Ampaque'. Evaluate patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics periodically to decide whether the dosage could be reduced or therapy discontinued. Antiemetic effect may mask signs of overdosage of other drugs or obscure diagnosis and treatment of conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see Warnings). When used concomitantly, may obscure vomiting as a sign of toxicity of a cancer chemotherapeutic agent. Discontinue high-dose, long-term therapy gradually. Patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics should be evaluated periodically for possible adjustment or discontinuance of drug therapy.

Adverse Reactions: Drowsiness; cholestatic jaundice; agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura and pancytopenia; postural hypotension, tachycardia, fainting, dizziness and occasionally a shock-like condition; reversal of epinephrine effects; EKG changes have been reported; neuromuscular (extrapyramidal) reactions: dystonias, motor restlessness, pseudo-parkinsonism, persistent tardive dyskinesia, psychotic symptoms, catatonic-like states, cerebral edema; convulsive seizures; abnormality of the cerebrospinal fluid proteins; urticarial reactions and photosensitivity, exfoliative dermatitis, contact dermatitis; asthma, laryngeal edema, angioneurotic edema, and anaphylactoid reactions; lactation and breast engorgement (in females on large doses), false positive pregnancy tests, amenorrhea, gynecomastia; hyperglycemia, hypoglycemia, glycosuria; dry mouth, nasal congestion, constipation, adynamic ileus, urinary retention, priapism, miosis, mydriasis; after prolonged substantial doses, skin pigmentation, epithelial keratopathy, lenticular and corneal deposits and pigmentary retinopathy, visual impairment; mild fever (after large I.M. doses); hyperpyrexia; increased appetite and weight; a systemic lupus erythematosus-like syndrome; peripheral edema.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported but no causal relationship has been established.

How Supplied: Tablets: 10 mg., 25 mg. or 50 mg., in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 100 mg. and 200 mg., in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only).

Spansule® brand of sustained release capsules: 30 mg., 75 mg., 150 mg. or 200 mg., in bottles of 50 and 500; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 300 mg., in bottles of 50; in Single Unit Packages of 100 (intended for institutional use only).

Ampule: 1 mL and 2 mL (25 mg./mL.), in boxes of 10, 100 and 500.

Multiple-dose Vial: 10 mL (25 mg./mL.), in boxes of 1, 20 and 100.

Syrup: 10 mg./5 mL. in 4 fl. oz. bottles.

Suppositories: 25 mg. or 100 mg., in boxes of 12.

Concentrate: 30 mg./mL., in 4 fl. oz. bottles and in cartons of 36 bottles. 100 mg./mL., in 8 fl. oz. bottles, in cartons of 12.

* phenytoin, Parke-Davis.

† metizamide, Winthrop Pharmaceuticals.

BRS-TZ:L72

SK&F Smith Kline & French Laboratories
A SMITHKLINE BECKMAN COMPANY
PHILADELPHIA, PA 19101

© SmithKline Beckman Corporation, 1989

INDEX TO ADVERTISERS

JULY 1989

The publication of an advertisement in this journal does not imply endorsement of the product or service by the American Psychiatric Association.

AUSTEN RIGGS CENTERA15

THE CHILDREN'S CAMPUSA9

CIBA-GEIGY PHARMACEUTICALS
Treatment INDA23

DISTA PRODUCTS/DIV. OF ELI LILLY & CO.
ProzacA36-A38

DORSEY DIVISION/SANDOZ PHARMACEUTICALS
MellarilA28
PamelorA17

EMPLOYMENT OPPORTUNITIESA22, A26, A45

LEMMON COMPANY
OrapA33-A34

MARYLAND BANKA12

MCNEIL PHARMACEUTICAL
Haldol DecanoateA31-A32

MEAD JOHNSON PHARMACEUTICAL
DesyrelC4

MECTA CORPORATIONA15

MERRELL DOW PHARMACEUTICALS
NorpraminA29-A30

OXFORD UNIVERSITY PRESSA9

PSYCHIATRIC DIAGNOSTIC LABORATORIES
OF AMERICAA2

ROCHE LABORATORIES
ValiumA13-A15

ROERIG DIV./PFIZER, INC.
NavaneA6-A8
SinequanA24-A26

SMITH, KLINE, FRENCH LABS
StelazineA21-A22
ThorazineA39-A40

SOMATICS, INC.A9

THOMAS, CHARLES C., PUBLISHERSC3

WYETH-AYERST LABORATORIES
AtivanC2-A1
Ativan Injection IMA18-A20

THE AMERICAN JOURNAL OF PSYCHIATRY

Information for Contributors

GENERAL POLICIES

The requirements stated below are in accordance with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

Prior Publication

Manuscripts are accepted for consideration by the *American Journal of Psychiatry* with the understanding that they represent original material, have not been published previously, are not being considered for publication elsewhere, and have been approved by each author. Any form of publication other than an abstract of no more than 400 words constitutes prior publication. This includes components of symposia, proceedings, transactions, books (or chapters), articles published by invitation, or reports of any kind, regardless of differences in readership, as well as electronic data bases of public nature. Authors submitting manuscripts containing data or clinical observations already used in published papers or used in papers that are in press, submitted for publication, or to be submitted shortly should provide this information and copies of those papers to the Editor. An explanation of the differences between the papers should be included.

Copyright Transfer and Submission Approval

The *Journal* requires approval of manuscript submission by all authors in addition to transfer of copyright to the American Psychiatric Association so that the author(s) and the Association are protected from misuse of copyrighted material. A submission approval and copyright transfer form will be forwarded to authors along with a letter acknowledging receipt of their manuscript. Manuscripts will not receive a final decision until a completed form has been received in the editorial office.

In addition, authors must obtain letters of permission from publishers for use of extensive quotations (more than 500 words). The *Journal* does not publish tables or figures that have been previously published or submitted elsewhere.

Disclosure of Commercial Interests

All forms of support, including drug company support, must be acknowledged in the author's footnote (see "Acknowledgments" under the Title Page section). Also, authors must disclose in their cover letter any commercial or financial involvements that might present an appearance of a conflict of interest in connection with the submitted article, including but not limited to institutional or corporate affiliations not already specified in the author's footnote, paid consultancies, stock ownership or other equity interests, and patent own-

ership. At the Editor's discretion, this information may be shared with reviewers. Such involvements will not be grounds for automatic rejection of the manuscript. Should the article be accepted for publication, the Editor and the authors will consult on whether, and to what extent, this information should be included in the published article.

Patient Anonymity

Ethical as well as legal considerations require careful attention to the protection of a patient's anonymity in case reports and elsewhere. Identifying information such as names, initials, hospital numbers, and dates must be avoided. In addition, authors should disguise identifying information when discussing the characteristics and personal history of patients.

Informed Consent

Manuscripts that report the results of experimental investigation with human subjects must include a statement that informed consent was obtained after the procedure(s) had been fully explained. In the case of children, authors are asked to include information about whether the child's assent was obtained.

Review Process

All papers are reviewed to determine the originality, validity, and importance of content and conclusions. In addition to the regular review process, peer review for statistical content may be required for some manuscripts. This will be determined by the *Journal's* Statistical Editors. Authors will be sent reviewer comments that are judged to be useful to them. All reviewers remain anonymous. Once the Editor has made a final decision on a paper, the authors of that paper will be informed.

SUBMISSION OF MANUSCRIPTS

The original manuscript and four copies should be submitted to John C. Nemiah, M.D., Editor, *American Journal of Psychiatry*, 1400 K St., N.W., Washington, DC 20005. All correspondence will be sent to the first-named author unless otherwise specified. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the *Journal* it is being submitted (i.e., Special Article, Regular Article, or Clinical and Research Report); papers will only be reviewed after such a statement has been received from the author.

Authors will be notified of the receipt of their paper and

INFORMATION FOR CONTRIBUTORS

the number assigned to it. **This number must be included in all further correspondence.** It is imperative that the corresponding author of submitted papers notify the *Journal* of changes of address. Because of escalating postage costs, no manuscripts submitted to the *Journal* will be returned to authors except upon special request. Authors must make this request in their original submission letter and include a self-addressed, postage-paid envelope.

Single Case Reports

Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. All single case reports will be peer reviewed. Reports of successfully treated patients must include data on the number of patients treated unsuccessfully by the same method, with an indication of the temporal order of the successes and failures.

Annual Meeting Papers

Authors may submit their papers before the annual meeting, but such papers cannot be published until after the meeting. All papers must be accompanied by a statement that they are in final form. These papers are subject to the same peer review as other papers and must conform to the requirements for one of the types of articles specified in the next section.

TYPES OF ARTICLES

Special Articles

These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including an abstract of no more than 100 words, tables, and figures) and may not include more than 100 references.

Regular Articles

Regular Articles are original communications of scientific excellence in psychiatric medicine and advances in clinical research. Regular Articles contain no more than 3,800 words, including an abstract of no more than 100 words, references, tables, and figures. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. Articles that exceed 3,800 words will be returned unreviewed to the authors.

Clinical and Research Reports

Clinical and Research Reports may contain no more than one table and a maximum of 10 references; figures may not be used. Papers may contain a **maximum** of 1,300 words, including an abstract of no more than 40 words, references, and an optional table (estimate 15 words per reference, 100 words for a double-spaced table that fills one-half of a vertical page, and 150 words for a double-spaced table that fills one-half of a horizontal page). These articles present 1) new research findings, 2) data from pilot studies, 3) worthwhile

replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

Other Sections

Letters to the Editor. Brief letters (maximum of 500 words and 5 references; no tables or figures) will be considered if they include the notation "for publication." Letters critical of an article published in the *Journal* will automatically be sent to the authors for reply. Because of space limitations not all letters can be printed. The *Journal* will notify authors about the disposition of their letters but does not return those that are not published. A letter must be signed by all of its authors. All letters will be edited; edited letters will not be sent to authors for approval. Letters must be typed double-spaced throughout on 8½×11 inch paper; three copies are required. Letters that do not meet these specifications will be returned for revision. Reprints are not available. **Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. Case reports submitted as Letters to the Editor will be peer reviewed.**

Book Forum. Books for review may be sent to the Book Forum Editor, Nancy C. Andreasen, M.D., Ph.D., University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242. Book reviews are usually solicited by the Book Forum Editor. Authors interested in reviewing a particular book should communicate directly with Dr. Andreasen. Reprints of reviews are not available.

TYPING AND ARRANGING THE PAPER

All parts of the manuscript, including case reports, quotations, references, and tables, must be **double-spaced** throughout. Manuscripts must be typed in upper- and lowercase on one side only of 8½×11 inch **nonerasable** bond paper. All four margins must be 1½ inches. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) references, and 5) tables and/or figures. All pages must be numbered.

STYLE SPECIFICATIONS

Title Page

Title. The title should be informative and as brief as possible. Two-part titles should be avoided.

By-line. Authors listed in the by-line should be limited to principal researchers and/or writers; collaborators may be acknowledged in a footnote. Authors' first names are preferred to initials. Degrees should be included after each author's name.

Previous presentation. If the paper has been presented at a meeting, please give the name of the meeting, the place, and the date.

Location of work and address for reprints. Provide the department, institution, city, and state where the work was done. Include a full address for the author who is to receive reprint requests.

Acknowledgments. Grant support should be acknowledged in a separate paragraph and should include the full

name of the granting agency and grant number. The *Journal* does not allow acknowledgment of persons involved with the preparation or typing of manuscripts. Acknowledgment of individuals involved with the scientific content of the work should not exceed four typed lines. Drug company support of any kind must be acknowledged.

Abstract

The abstract is a single paragraph no longer than 100 words for Special Articles and Regular Articles and no longer than 40 words for Clinical and Research Reports.

Text

Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

Research design and statistics. The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. All significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ($F=4.32$, $df=3, 17$, $p<0.05$).\" Reviewers will evaluate the appropriateness of the analyses.

Abbreviations. Spell out all abbreviations (other than those for units of measure) the first time they are used. Idiosyncratic abbreviations should not be used.

Drugs. Generic rather than trade names of drugs should be used. Trade or manufacturers' names are used only if the drug or equipment is experimental or unavailable in this country or if such information is crucial to the evaluation of the results or replication of the study.

References

References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. Do not arrange the list alphabetically. References in tables and figures are numbered as though the tables and figures were part of the text.

References should be restricted to closely pertinent material. Accuracy of citation is the author's responsibility. References should conform exactly to the original spelling, accents, punctuation, etc. Authors should be sure that all references listed have been cited in text.

Personal communications, unpublished manuscripts, manuscripts submitted but not yet accepted, and similar unpublished items should not appear in the reference list. Such citations may be noted in text. It is the author's responsibility to obtain permission to refer to another individual's unpublished observations. Manuscripts that are actually "in press" may be cited as such in the reference list; the name of the journal or publisher and location must be included.

Type references in the style shown below, double-spaced throughout. List up to three authors; designate one or more authors past the third as "et al." Abbreviations of journal names should conform to the style used in *Index Medicus*; journals not indexed there should not be abbreviated.

1. Noyes R Jr, DuPont RL Jr, Pecknold JC, et al: Alprazolam in panic disorder and agoraphobia, results from a multicenter trial, II: patient acceptance, side effects, and safety. *Arch Gen Psychiatry* 1988; 45:423-428
2. Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry*, 4th ed, vol 2. Baltimore, Williams & Wilkins, 1985
3. Fyer AJ, Manuzza S, Endicott J: Differential diagnosis and assessments of anxiety: recent developments, in *Psychopharmacology: The Third Generation of Progress*. Edited by Meltzer HY. New York, Raven Press, 1987

TABLES AND FIGURES

The *Journal* does not publish tables or figures that have been submitted elsewhere or previously published. Table and figures that duplicate 1) material contained in text or 2) each other will not be used. Authors will be asked to delete tables and figures that contain data which could be given succinctly in text. Each table and figure should be understandable without reference to the text; a descriptive, concise title should be included and units of measurement should be specified. Consult recent issues of the *Journal* for format. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. A copy of each table and figure must be included with each copy of the manuscript.

Tables

Tables should be double-spaced, no wider than 120 type writer characters, including spaces, and no longer than 70 lines. Values expressed in the same unit of measurement should read down, not across; when percentages are given the appropriate numbers must also be given.

Figures

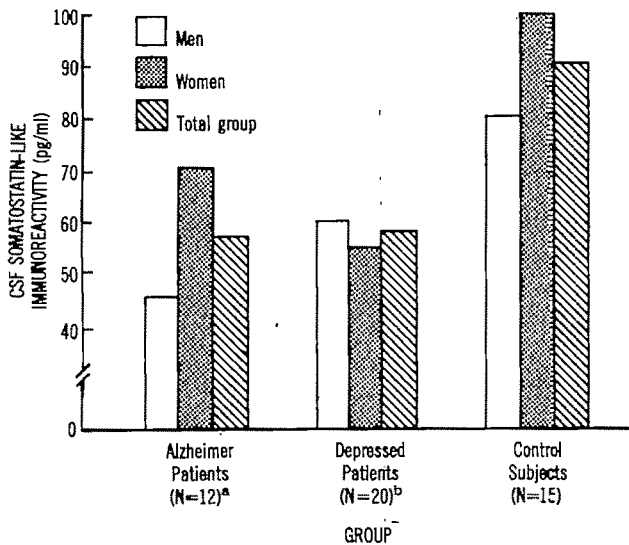
Figures are considered as text and are subject to revision by the authors upon recommendation of the Editors. Figure should, however, be professionally prepared. Glossy or other camera-ready prints should accompany the submitted manuscript. Computer-generated figures that do not meet quality printing standards will be returned for revision. The first author's name, the title of the paper, the figure number, and the top of the figure should be noted on a label affixed to the back of each figure. All figure titles and footnotes should be typed and sent together on a separate page.

The *Journal* does publish color illustrations. However, the cost to publish them, including reprint charges, will be the responsibility of the authors. An estimate of the cost will be provided to the authors at the time of first decision.

Format. Figures are visual expressions of data trends or relationships. Figures that represent numerical data which could be expressed more succinctly or clearly in tabular form should be converted to tables. Line graphs should show change in continuous variables; comparisons of like values in different groups should be presented as bar graphs. Graphs containing stacked bars are unacceptable; the different segments of each bar should be presented side by side.

Lettering. Figure type should be sans serif and should be large enough to remain legible after the figure is reduced. Most figures taking up the width of a vertical manuscript page are reduced to a width of 19.5 picas (3¼ inches), and those requiring a horizontal manuscript page are usually reduced to 40.5 picas (6¾ inches). When space on the hori-

FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



^aSignificant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).

^bSignificant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

zontal axis is insufficient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

Other: The following are additional specific requirements. Please refer to the example given above.

1. Do not use solid black shading; rather, include outlined white among shadings.
2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.
3. Error bars should not be used.
4. Do not extend the vertical or horizontal axis of a graph beyond the point needed for the data shown.
5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.

6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.

7. To save space, related figures that have the same vertical or horizontal axis should be combined. Headings identifying the segments of the combined figure should appear in the upper lefthand corners of the individual segments (in lower-case type with an initial upper-case letter).

8. The key should appear within or above the figure but should not be wider than the figure itself. Avoid placing other type (e.g., number of subjects, statistical values) within the axes of a graph.

9. Footnotes (including p values) should be cited with superscript letters in the title or body of the figure and should be listed in the order in which they are cited in the figure.

PROCESSING OF ACCEPTED MANUSCRIPTS

Manuscripts are accepted with the understanding that the Editor and the editorial staff have the right to make revisions aimed at greater conciseness, clarity, and conformity with *Journal* style. Accepted papers will be edited and sent to the first-named (or corresponding) author for corrections and answers to editorial queries. No proofs are sent to authors. Authors who will be away from their offices for a long period or who change address after notification of acceptance should inform the *Journal* staff.

PERMISSION TO REPRINT

Written permission to reprint material published in the *Journal* must be secured from the APA Periodicals Services Division, 1400 K Street, N.W., Washington, DC 20005; telephone: (202)682-6156. There is usually a charge for such permission, except for nonprofit classroom or library reserve use by instructors and educational institutions or for authors who wish to reprint their own material. Requests will be facilitated if accompanied by written permission from the author of the material.

REPRINTS

No reprints are furnished gratis. An order form for reprints will be sent to the corresponding author before publication of the paper. The printer usually mails reprints approximately 6 weeks after the article has been published. Reprints of items in the Book Forum and Letters to the Editor sections are not available.

CHILD AND ADOLESCENT PSYCHIATRIST

Part-time position available to work approximately 20 hours per week for a progressive Community Mental Health Center in Camp Hill, PA. In addition to the inpatient case load, a private practice is encouraged. An excellent support staff is available. Responsibilities include: evaluations, outpatient medication, consults and inservice training. Applicants should be PA licensed or eligible. Excellent salary and pro-rated benefits.

Our mental health center is part of Holy Spirit Hospital and is located in beautiful South Central PA. Camp Hill is situated in an attractive tree-lined commercial complex just across the river from the state capitol. The area offers many local attractions for varied interests (Hershey Park, skiing, golfing, historical attractions, and the Harrisburg Symphony and theatre entertainment).

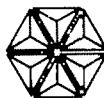
Qualified applicants may send a resume to
Holy Spirit Hospital
N. 21st Street
Camp Hill, PA 17011
ATTN: Mr. C. Rustici

ASSISTANT DIRECTOR OF CLINICAL STUDIES, CENTRAL NERVOUS SYSTEM

Bristol-Myers U.S. Pharmaceutical and Nutritional Group, headquartered in southern Indiana, has a key challenge in its Medical Department. You will manage and monitor a number of projects simultaneously, participate in protocol development, and monitor various clinical studies. Involves maintaining a strong interface with the academic community.

The position requires an individual with a PharmD or PhD in Pharmacology/Psychology or an equivalent biological science, and a minimum of two years of industry experience (preferably in neuropharmacology research/clinical studies).

Bristol-Myers offers a competitive salary, excellent fringe benefits, liberal relocation assistance, and an environment with outstanding opportunities for career growth. Send your resume and a letter indicating why your background and experience are a match for the position to: **Manager, Professional Employment, Dept. 8K65, BRISTOL-MYERS U.S. PHARMACEUTICAL AND NUTRITIONAL GROUP, 2400 W. Lloyd Expressway, Evansville, IN 47721.** An equal opportunity employer m/f/h/v.



A Bristol-Myers Company

U.S. PHARMACEUTICAL AND
NUTRITIONAL GROUP

Chairman Department of Psychiatry and Behavioral Sciences Baylor College of Medicine Chief of Psychiatry The Methodist Hospital

Baylor College of Medicine and The Methodist Hospital, Houston, are seeking an individual for the joint appointment as the departmental Chairman and Chief of Psychiatry Service. Candidates must be Diplomates of the American Board of Psychiatry and Neurology, possess the academic credentials for appointment or promotion to Professor of Psychiatry and Behavioral Sciences, and have the ability to develop superior programs in basic and clinical research, education, and clinical service in psychiatry. Applicants should submit a curriculum vitae to:

Dan B. Jones, M.D., Chairman,
Search Committee for
Chairman/Chief of Psychiatry
Cullen Eye Institute
6501 Fannin, NC 200
Houston, Texas 77030

Baylor College of Medicine and The Methodist Hospital are
Affirmative Action/Equal Opportunity Employers.

DIRECTOR

Unique growth opportunity for ambitious candidates who want to see far-reaching results from their contributions. The Department of Psychiatry of UAMS is seeking a Director for its University Hospital Division. Position is key to realizing strategic goals and will lead the department in developing new private services and capitalizing on the clinical services currently available.

We encourage senior clinicians and aspiring junior clinicians with strong management and leadership skills, proven teaching expertise, and a background in service systems to consider this opportunity. It should be particularly attractive to private sector practitioners who want to return to a stimulating academic setting.

Compensation is very competitive. In addition, we are located in a low cost-of-living, high quality-of-life area with an attractive blend of urban amenities and rural beauty.

For further information, please call or write, in strict confidence, to:

G. Richard Smith, M.D., Vice Chairman for Research
University of Arkansas
for Medical Sciences
4301 W. Markham — Slot 554
Little Rock, Arkansas 72205
(501) 686-5600



Psychological Medicine

Volume 19 Number 2 May 1989

EDITORIALS

- Caution in locating the gene(s) for
affective disorder J.H. EDWARDS AND
D.C. WATT 273
- Panic disorder: fact or fiction?
M.G. GELDER 277
- Schizophrenia: fixed incidence or fixed
thinking? E.F. TORREY 285

ORIGINAL ARTICLES

- SMITH, R. Expertise, procedure and the
possibility of a comparative history of
forensic psychiatry in the nineteenth
century 289
- TURNER, T.H. Schizophrenia and mental
handicap: an historical review, with
implications for further research 301
- GUZE, S.B. Biological psychiatry: is there
any other kind? 315
- BAKER, H.F., RIDLEY, R.M., CROW, T.J. AND
TYRELL, D.A.J. A re-investigation of the
behavioural effects of intracerebral
injection in marmosets of cytopathic
cerebrospinal fluid from patients with
schizophrenia or neurological disease 325
- CHARLTON, B.G. AND FERRIER, I.N.
Hypothalamo-pituitary-adrenal axis
abnormalities in depression: a review and
a model 331
- ROSSI, A., STRATTA, P., D'ALBENZIO, L.,
DI MICHELE, V., SERIO, A., GIORDANO, L.,
PETRUZZI, C. AND CASACCHIA, M.
Quantitative computed tomographic
study in schizophrenia: cerebral density
and ventricle measures 337
- COURSEY, R.D., LEES, R.W. AND
SIEVER, L.J. The relationship between
smooth pursuit eye movement
impairment and psychological measures
of psychopathology 343
- FRITH, C.D. AND DONE, D.J. Experiences
of alien control in schizophrenia reflect a
disorder in the central monitoring of
action 359
- ANGERMEYER, M.C., GOLDSTEIN, J.M. AND
KUEHN, L. Gender differences in
schizophrenia: rehospitalization and
community survival 365
- BURNS, A., MARSH, A. AND BENDER, D.A.
Dietary intake and clinical,
anthropometric and biochemical indices
of malnutrition in elderly demented
patients and non-demented subjects 383
- BEBBINGTON, P., KATZ, R., MCGUFFIN, P.,
TENNANT, C. AND HURRY, J. The risk of
minor depression before age 65: results
from a community survey 393
- WILHELM, K. AND PARKER, G. Is sex
necessarily a risk factor to depression? 401
- COOPER, C.L., COOPER, R. AND
FARAGHER, E.B. Incidence and

- perception of psychosocial stress: the
relationship with breast cancer 415
- NILSSON, L-G., BÄCKMAN, L. AND
KARLSSON, T. Priming and cued recall in
elderly, alcohol intoxicated and sleep
deprived subjects: a case of functionally
similar memory deficits 423
- PARKER, G., HAYWARD, L. AND JOHNSON, P.
Factorial validity of the EE scales 435
- HERMELIN, B., O'CONNOR, N., LEE, S. AND
TREFFERT, D. Intelligence and musical
improvisation 447
- ALLEN, C.I., GILLESPIE, C.R. AND
HALL, J.N. A comparison of practices,
attitudes and interactions in two
established units for people with a
psychiatric disability 459
- ANDRICH, D. AND VAN SCHOU BROECK, L.
The General Health Questionnaire: a
psychometric analysis using latent trait
theory 469
- JORM, A.F., DUNCAN-JONES, P. AND
SCOTT, R. An analysis of the re-test
artefact in longitudinal studies of
psychiatric symptoms and personality 487
- CHONG, M-Y. AND WILKINSON, G.
Validation of 30- and 12-item versions of
the Chinese Health Questionnaire (CHQ)
in patients admitted for general health
screening 495
- KITAMURA, T., SUGAWARA, M., AOKI, M. AND
SHIMA, S. Validity of the Japanese
version of the GHQ among antenatal
clinic attendants 507

PRELIMINARY COMMUNICATION

- Development of a new self-report
questionnaire to measure self esteem
P. ROBSON 513

BRIEF COMMUNICATION

- Gun ownership and suicide in the United
States D. LESTER 519

BOOK REVIEWS

- Classification of Mental Disorder in
Primary Care* D.L. CROMBIE 523
- The Neuropathology of Temporal Lobe
Epilepsy* D.C. TAYLOR 525
- Computer Applications in
Psychiatry* D.J. HAND 527
- Receptors and Ligands in
Psychiatry/Receptors and Ligands in
Neurological Disorders* I. CAMPBELL 527
- Biological Council Symposium on Drug
Action. Excitatory Amino Acids in
Health and Disease* R.M. MARCHBANKS 528

- SHORT REVIEWS 529
- PSYCHIATRY IN THE 1880S 537

CHARLES C THOMAS • PUBLISHER

=== NEW! ===

- Morse, H. Newcomb—**COMMENTARY ON LEGAL PSYCHIATRY.** '89, 300 pp. (7 x 10), about \$47.75.

=== NEW! ===

- Malcolm, John Gulton—**TREATMENT CHOICES AND INFORMED CONSENT: Current Controversies in Psychiatric Malpractice Litigation.** '88, 136 pp. (7 x 10), \$30.75.

=== NEW! ===

- Mendelson, George—**PSYCHIATRIC ASPECTS OF PERSONAL INJURY CLAIMS.** '88, 296 pp. (7 x 10), 3 il., 5 tables, \$43.75.

=== NEW! ===

- Thyer, Bruce A.—**BEHAVIORAL FAMILY THERAPY.** '89, 352 pp. (7 x 10), 11 il., 7 tables, about \$56.75.

=== NEW! ===

- Bierker, Susan B.—**ABOUT SEXUAL ABUSE.** '89, 316 pp. (7 x 10), about \$49.75.

=== NEW! ===

- Verville, Elinor—**HABIT.** '88, 280 pp. (7 x 10), \$32.75.

=== NEW! ===

- Milgram, Roberta M.—**TEACHING GIFTED AND TALENTED LEARNERS IN REGULAR CLASSROOMS.** '89, 330 pp. (7 x 10), 25 il., 3 tables, about \$49.75.

=== NEW! ===

- Lentz, John D.—**EFFECTIVE HANDLING OF MANIPULATIVE PERSONS.** '89, 110 pp. (7 x 10), 7 il., about \$25.75.

- Grinker, Roy R., Sr. & Martin Harrow—**CLINICAL RESEARCH IN SCHIZOPHRENIA: A Multidimensional Approach.** '87, 436 pp. (7 x 10), 15 tables, \$60.50.

- Forrest, Gary G.—**INTENSIVE PSYCHOTHERAPY OF ALCOHOLISM.** '84, 230 pp., 1 table, \$29.75.

- Forrest, Gary G.—**ALCOHOLISM AND HUMAN SEXUALITY.** '83, 408 pp., \$43.25.

- Forrest, Gary G.—**ALCOHOLISM, NARCISSISM AND PSYCHOPATHOLOGY.** '83, 320 pp., 1 table, \$34.75.

- Forrest, Gary G.—**THE DIAGNOSIS AND TREATMENT OF ALCOHOLISM.** (2nd Ed.) '78, 362 pp., 7 tables, \$30.00, spiral (paper).

=== NEW! ===

- Sadoff, Robert L.—**FORENSIC PSYCHIATRY: A Practical Guide for Lawyers and Psychiatrists.** (2nd Ed.) '88, 262 pp. (7 x 10), \$43.75.

=== NEW! ===

- Kantor, Martin—**DETERMINING MENTAL STATUS: The "Physical Examination" of Psychiatry.** '88, 502 pp. (7 x 10), \$75.50.

=== NEW! ===

- Gregg, Charles H., Judy L. Robertus & J. Blair Stone—**THE PSYCHOLOGICAL ASPECTS OF CHRONIC ILLNESS.** '89, 384 pp. (7 x 10), 7 il., 15 tables, about \$

=== NEW! ===

- Crespi, Tony D.—**CHILD AND ADOLESCENT PSYCHOPATHOLOGY AND INVOLUNTARY HOSPITALIZATION: A Handbook for Mental Health Professionals.** '89, 150 pp. (7 x 10), 1 table, about \$31.75.

=== NEW! ===

- Lindley, Mary E.—**A MANUAL ON INVESTIGATING CHILD CUSTODY REPORTS.** '88, 194 pp. (7 x 10), \$32.75.

=== NEW! ===

- Knudsen, Dean D.—**CHILD PROTECTIVE SERVICES: Discretion • Decisions • Dilemmas.** '88, 230 pp. (7 x 10), 3 il., 34 tables, \$36.75.

=== NEW! ===

- Johann, Sara Lee & Frank Osanka—**REPRESENTING... BATTERED WOMEN WHO KILL.** '89, 414 pp. (7 x 10) about \$64.75.

=== NEW! ===

- MacHovec, Frank J.—**INTERVIEW AND INTERROGATION: A Scientific Approach.** '89, 188 pp. (7 x 10), about \$34.75.

- Miller, Robert D.—**INVOLUNTARY CIVIL COMMITMENT OF THE MENTALLY ILL IN THE POST-REFORM ERA.** '87, 280 pp. (7 x 10), \$47.25.

- Cohen, Richard L. & Mina K. Dulcan—**BASIC HANDBOOK OF TRAINING IN CHILD AND ADOLESCENT PSYCHIATRY.** '87, 532 pp. (7 x 10), 1 il., 10 tables, \$75.75.

- Jacobsen, Jamia Jasper—**PSYCHIATRIC SEQUELAE OF CHILD ABUSE: Reconnaissance of Child Abuse and Neglect—Evaluation, Prospects, Recommendations.** '86, 230 pp. (7 x 10), 4 il., 6 tables, \$32.25.

Books sent on approval • Catalog sent on request • Write or call (217) 789-8980

2600 South First Street Springfield • Illinois • 62794-9265

GIVE YOUR PATIENTS A BREAK



Desyrel Dividose 150 mg and 300 mg tablets

- More convenient.
- Easy to titrate — each tablet contains 4 dosage strengths in one convenient tablet.
- More economical than other forms of Desyrel.

Desyrel[®] **DIVIDOSE[®]**
(trazodone HCl) 150 mg and 300 mg tablets

MeadJohnson
PHARMACEUTICALS



A Bristol-Myers Company
Evansville, Indiana 47721
U.S.A.